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## Original Communications

### HEART DISEASE IN THE ARGENTINE*

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THE important and useful activity developed by United States investigators during the last few years has had great influence on the progress of medical knowledge everywhere, and the repercussions thereof in the Argentine have been so great that, today, North American medical literature predominates above that from all other countries, quite contrary to the situation in the past.

In respect to heart disease, this influence has been even more marked in my country, so much so, that the nomenclature and criteria for its diagnosis, as adopted by the American Heart Association, is used in every heart clinic, and the textbook written by the president, Paul D. White, has the greatest circulation and respect in the field of cardiology.

As a consequence, for the last few years, 90 per cent of our physicians who have gone to study abroad have chosen the United States; that is how I came to New York in 1936, and I had the good fortune to see for myself, and appreciate, that exceptionally clear-sighted man, Lewis A. Conner, whose name has been given to this special lecture on cardiovascular problems.

Now I have come again to the United States to give the Conner Lecture on heart disease in the Argentine. This quite unexpected honor is deeply appreciated by me, and should be interpreted as a generous act on the part of the American Heart Association to the investigators of heart disease in my country. This, indeed, is handsome proof of the human solidarity which binds us together more than ever in these days that challenge traditional American liberty.

#### PUBLIC HEALTH PROBLEMS

The Public Health Service of my country, on several occasions (Sussini and Cossio,[1] and Spangenberg[2]), has considered heart disease as one of the fundamental problems of public health. This is due not only

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to its wide incidence in all walks of life, but also to the gravity of the economic loss to the community.

Macera and Ruchelli[3] found organic heart disease in 2.4 per cent of 10,000 school children. Bocalandro, Carrón, and Segura[4] also found heart disease in 1.4 per cent of 6,806 soldiers who were 20 years old. Rodriguez[5] found heart disease in 3 per cent of railway employees whose average age was 35 years. If these rates are taken in relation to the various age groups of the Argentine population, it must be accepted that, among the 13,000,000 inhabitants of my country, there are approximately 2 per cent with heart disease, that is to say, a total of 260,000 (Table I).

TABLE I

INCIDENCE OF HEART DISEASE IN THE ARGENTINE

| | INCIDENCE (PER CENT) |
|---|---|
| School children | 2.4 |
| Soldiers | 1.4 |
| Railway employees | 3.0 |

Population: 13,000,000.
Population with heart disease: 260,000.
Heart disease incidence: 2 per cent.

The official statistics of mortality show that heart disease is the chief cause of death. The average number of deaths today in my country is 161,223 per year, of which 26,068 are caused by heart disease, 24,909 by pulmonary disease exclusive of tuberculosis, 17,531 by disease of the gastrointestinal tract, 13,850 by tuberculosis, 10,813 by cancer, 10,604 by disease of the nervous system, 8,921 by infectious diseases, excluding tuberculosis, and the remaining 49,987 by various other diseases. These incidences signify the following percentages in mortality: heart disease, 16 per cent; pulmonary disease, excluding tuberculosis, 15 per cent; gastrointestinal disease, 11 per cent; tuberculosis, 9 per cent; cancer, 7 per cent; nervous system disease, 6 per cent; infectious diseases, excluding tuberculosis, 5 per cent, and other diseases, 31 per cent (Table II).

TABLE II

MORTALITY (ABSOLUTE AND PER CENT) IN THE ARGENTINE REPUBLIC AND IN BUENOS AIRES

| | ARGENTINE REPUBLIC | | BUENOS AIRES | |
|---|---|---|---|---|
| | ABSOLUTE | PER CENT | ABSOLUTE | PER CENT |
| Heart disease | 26,068 | 16 | 6,894 | 24 |
| Cancer | 10,813 | 7 | 4,286 | 15 |
| Pulmonary disease, excluding tuberculosis | 24,909 | 15 | 3,064 | 11 |
| Tuberculosis | 13,850 | 9 | 2,748 | 10 |
| Disease of the nervous system | 10,604 | 6 | 2,485 | 9 |
| Gastrointestinal disease | 17,531 | 11 | 2,273 | 8 |
| Infections, excluding tuberculosis | 8,921 | 5 | 1,212 | 4 |
| Other causes | 49,987 | 31 | 5,565 | 19 |

The predominance of heart disease in the mortality of my country is still greater if one takes into account only the deaths in the cities. For example, in Buenos Aires the deaths numbered 28,537 during 1940; 6,894 were from heart disease, 4,286 from cancer, 3,064 from nontuberculous pulmonary disease, 2,748 from tuberculosis, 2,485 from nervous system disease, 2,273 from gastrointestinal disease, 1,212 from infectious diseases, excluding tuberculosis, and 5,565 from other causes. These incidences give the following percentages: heart disease, 24 per cent; cancer, 15 per cent; pulmonary disease, excepting tuberculosis, 11 per cent; tuberculosis, 10 per cent; nervous system disease, 9 per cent; gastrointestinal disease, 8 per cent; infectious diseases, excluding tuberculosis, 4 per cent; and several other causes, 19 per cent (Table II).

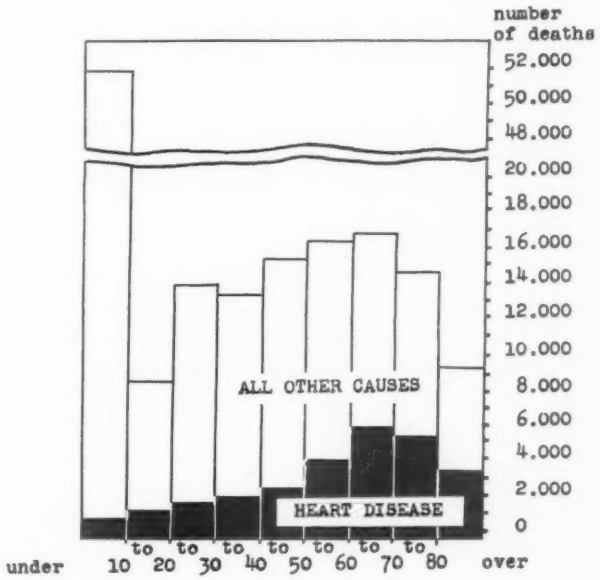


Fig. 1.—Deaths from heart disease compared with deaths from all other causes, by decades, in the Argentine.

The predominance of deaths from heart disease in the mortality of the cities over the mortality of the whole country shows that heart disease is more frequent in the cities than in the country districts. The greater incidence in the cities is due partly to the greater frequency of deaths from pneumonia and gastrointestinal disease in the country districts, and partly to its actually greater frequency in the cities; so that, today, the death rate from heart disease is 280 per 100,000 inhabitants, and, in the whole country, only 213 per 100,000 inhabitants.

The mortality from heart disease shows a significant difference according to age. More than one-half of the deaths, namely, 60 per cent, occur in people over 60 years of age, 24 per cent among those 40 to 60 years

of age, 11 per cent among those 20 to 40 years old, and only 5 per cent in those under 20 years of age.

If this mortality from heart disease is compared to all other causes according to age groups, it will be seen that 1 in every 3 deaths is from heart disease in people over 60 years of age, and, in every 5 deaths, 1

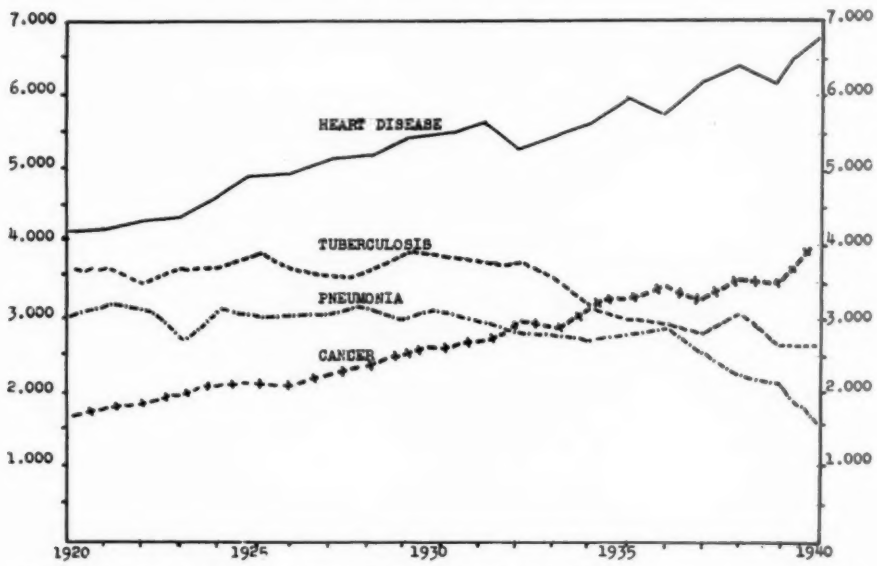


Fig. 2.—Deaths from heart disease, cancer, tuberculosis, and lobar pneumonia in Buenos Aires annually from 1920 to 1940 inclusive.

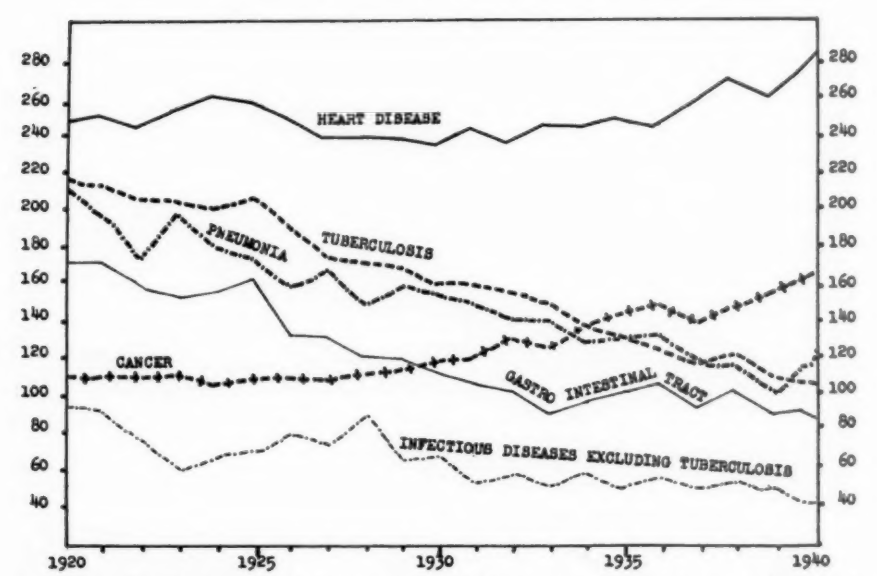


Fig. 3.—Deaths from heart disease, tuberculosis, cancer, pneumonia, gastrointestinal disease, and infectious diseases (per hundred thousand inhabitants) in Buenos Aires annually from 1920 to 1940.

is from heart disease in those between 40 and 60 years of age, whereas, in people of 20 to 40 years of age, only 1 out of 9 deaths is from heart disease, and among those under 20 years of age, 1 out of 60 is from heart disease (Fig. 1).

The predominance of heart disease in the mortality of my country has gradually become a fact during the last few years, first, by its absolute increase, and, second, as a result of lessening of some of the other causes, especially infectious diseases, including pneumonia and tuberculosis, as well as gastrointestinal diseases.

In 1920, in Buenos Aires, 4,100 persons died from heart disease (Figs. 2 and 3), which is 254 out of every 100,000 inhabitants; now the deaths number 6,894, which is 280 out of every 100,000 inhabitants.

In the same year, 1920, on the contrary, there were 214 deaths per 100,000 from tuberculosis; 213 per 100,000 from lung disease, excluding tuberculosis; 165 per 100,000 from gastrointestinal disease; and 91 per 100,000 from other infectious diseases, whereas, today, there are 110 per 100,000 from tuberculosis; 120 per 100,000 from pulmonary disease, excluding tuberculosis; 90 per 100,000 from gastrointestinal disease, and 5 per 100,000 from other infectious diseases.

It is not possible to know with any exactness the economic losses caused by heart disease, but, to give some idea, it is enough to say that 40 per cent of the pensions paid to invalids in the whole country are drawn by people with heart disease. The Civil Service Pension Board for the 300,000 government employees pays 6,000,000 Argentine paper dollars annually for heart disease incapacity alone. The Railway Pension Board for the 140,000 employees paid, during the last 18 years, 32,000,000 Argentine paper dollars for heart disease incapacity. It has been calculated that the pecuniary losses occasioned by heart disease in my country are more than 100,000,000 Argentine paper dollars per year, including medical attention and virtual salaries.

The causes of heart disease in the Argentine are the same as in other countries, but with different predominances occasioned by climate, habits, and other unknown factors.

The city of Buenos Aires, with 2,500,000 inhabitants and ways of living common to all big cities, is situated at south latitude 35°, with a temperate, but damp, climate. The causes of heart disease, according to clinical, radiologic, and electrocardiographic studies of 10,000 patients (4,000 private cases and 6,000 hospital cases, the last including more than 400 autopsies), are as follows: coronary insufficiency, 29.6 per cent; infectious disease, 28.1 per cent; rheumatism, 18.2 per cent; syphilis, 7.7 per cent; arterial hypertension, 27.5 per cent (systemic, 23.7 per cent, pulmonary, 3.7 per cent); thyrotoxicosis, 5.8 per cent; trauma, wounds, and other causes, 4.9 per cent; congenital anomalies, 2.4 per cent; and unknown causes, 1.5 per cent (Table III).

TABLE III

THE RELATIVE INCIDENCE OF THE PRINCIPAL ETIOLOGIC TYPES OF ORGANIC HEART DISEASE IN SEVERAL CITIES OF THE ARGENTINE

| | CASES | CONGENITAL (PER CENT) | RHEUMATISM (PER CENT) | SYPHILIS (PER CENT) | CORONARY (PER CENT) | HYPERTENSION (PER CENT) | COR PULMONALE (PER CENT) | THYROID (PER CENT) | OTHER CAUSES (PER CENT) |
|---|---|---|---|---|---|---|---|---|---|
| Buenos Aires (Cossio) | 10,000 (6,000 hospital and 4,000 private) | 2.4 | 18.2 | 7.7 | 29.6 | 23.7 | 3.7 | 5.8 | 8.9 |
| Rosario (Gonzalez Sabathié) | 4,500 (3,000 hospital and 1,500 private) | 2.5 | 18.4 | 9.0 | 20.0 | 36.4 | 1.6 | 3.3 | 8.8 |
| Mendoza (Castro Aubone) | 3,594 (3,279 hospital and 314 private) | 1.5 | 25.0 | 6.8 | 23.0 | 39.6 | 0.9 | 1.2 | 2.0 |

This incidence is modified by age. Arana and Kreutzer,[6] in studying 1,500 children with organic heart disease, found rheumatism in 60 per cent, congenital anomalies in 28 per cent, and several other causes in 12 per cent; that is to say, of 10 children, 6 had rheumatism, 3 congenital anomalies, and 1 heart disease of another kind. Between the ages of 20 and 40 years, rheumatism remained the chief cause in 4 out of 10 cases. After 40, the most important cause is coronary disease and arterial hypertension in the following proportions: in every 10 cases there are 4 of coronary disease, 3 of hypertension, and 3 of other diseases. After the age of 60, this proportion is greater, i.e., 6 of coronary disease, 3 of hypertension, and 1 of other diseases (Cossio and Campana[7]).

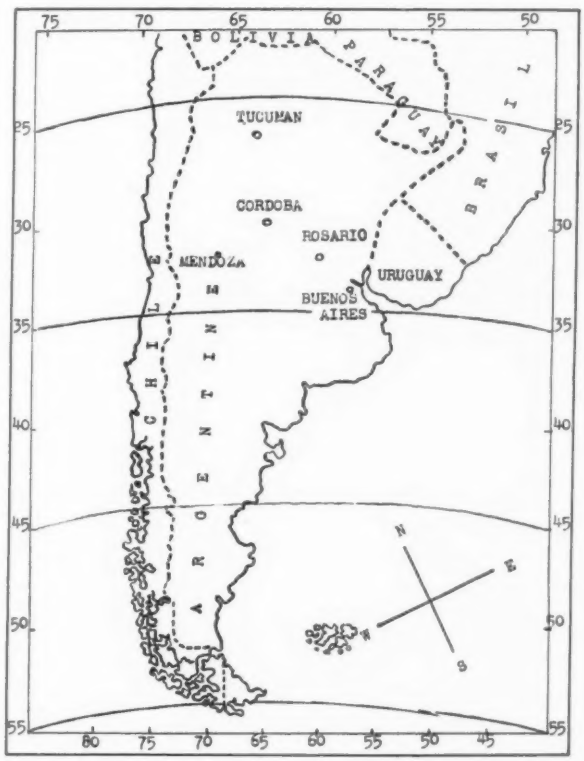


Fig. 4.

There is also a difference between private and hospital patients, depending upon their respective economic capacities. In private practice, rheumatism is slightly less frequent than among hospital patients, i.e., in the first, 17 per cent, and, in the second, 19 per cent, but, on the contrary, in private practice coronary disease, including angina pectoris, is much more common than among hospital patients; coronary disease among private patients represents 35.9 per cent, and, in the hospital group, 23.3 per cent.

It has been thought by some that a diet in which meat predominates is an important factor in atherosclerosis. Study of the causes of heart disease in the Argentine does not support this hypothesis, for the yearly consumption of meat per person is 107 kg. and the incidence of coronary disease is only 29.6, whereas, in the United States, the yearly consumption of meat per person is 66 kg. (Gomez[8]), and the incidence of coronary disease is 37.7 per cent (White and Jones[9]).

In other cities of my country (Fig. 4) the incidence of the causes of heart disease is similar to that in Buenos Aires, but with some differences according to the climate and the degree of commodities available. In Rosario, with its 500,000 people, and more or less the same climate but quieter living, Gonzalez Sabathié[10] found less coronary artery disease among 4,500 private and hospital patients. Castro Aubone[10] found more rheumatism among 3,594 patients in the city of Mendoza, which has a population of 83,000 but a colder winter. On the contrary, in Cordoba, with 273,000 inhabitants and a much warmer and drier climate, Maldonado Allende[10] found very much less rheumatism, i.e., only 11 per cent, but more syphilis, i.e., 17 per cent.

### MEDICAL TEACHING AND CARDIAC CLINICS

In 1930, Padilla and I organized, in the Physical Diagnostic Institute of the Medical School of Buenos Aires, the first postgraduate course on heart disease, which consisted of lectures and bedside teaching. Since then, other similar courses have been conducted in the Institute of Physiology and in the Ramos Mejia Hospital, also at Buenos Aires. During the last few years a postgraduate course in heart disease has been held in the Institute of Physiology of the Medical School of Cordoba. The result of these activities is that today there are in my country forty specialists in heart disease, all members of the Argentine Cardiological Society, which holds six meetings yearly in the chief hospitals of Buenos Aires. The *Argentine Heart Journal*, already in its ninth year, is the official organ of this society.

In some of the hospitals of Buenos Aires there are "cardiac clinics" and, in the others, "heart stations or laboratories" in charge of specialists in heart disease, with all the equipment necessary to make a complete diagnosis. In addition, each cardiac clinic has its own social service. The clinics have accommodations for inpatients and outpatients, the stations only for outpatients. Some cities in the interior, such as Rosario, Cordoba, Tucumán, and Mendoza, also have their own cardiac clinics or heart stations, which are organized like those in the city of Buenos Aires.

One of the cardiac clinics, for example, which is in my personal charge at the Medical School Hospital, has forty beds for cardiac patients. In addition to the regular diagnostic equipment, we have instruments for research work, such as apparatus for optical graphic and electrical

registration of heart sounds and arterial and jugular pulse, and for the estimation of cardiac output, blood and alveolar gases, blood volume, and so forth. Recently the Medical School received an important donation to endow an institution dedicated exclusively to cardiovascular investigation.

Likewise, the public health service has a department, also in my charge, for making the medical examinations that are necessary for the employees who are pensioned off for heart disease. This department also functions in the periodic health examinations of Government employees as a preventive measure against incapacity through heart disease.

## RESEARCH CONTRIBUTIONS

The first original contribution in the Argentine was the syndrome happily called by Ayerza,[11] in 1901, "cardiacos negros," meaning black cardiacs, consisting of hypercyanosis, dyspnea, and overstrain of the right ventricle, with edema. In the beginning there was some confusion about this syndrome; it was thought to have a specific cause, and was called primary sclerosis or syphilis of the pulmonary artery (Arrillaga[12]), hyperplasia of the marrow (Escudero[13]), and so on. Later, intensive studies have shown that the initial lesion is a chronic bronchopneumonia caused by a common infection, exceptionally by syphilis or tuberculosis, with or without pulmonary arterial sclerosis and obliteration of the smaller arteries and arterioles; this is followed by overstrain of the right ventricle, with myocardial failure, which is today called chronic cor pulmonale, but with the particular characteristic that cyanosis predominates because of a disturbance in the gaseous interchange in the lungs brought about by lessening of the tension of the alveolar oxygen, i.e., so-called alveolar hypoventilation, caused by loss of the pulmonary elasticity and an increase of the pulmonary dead space (Ayerza, Solari, and Berconsky,[14] Cossio and Berconsky,[15] and Capdehourat[16]).

Several other contributions have been made, but only a few will be mentioned.

In 1917, Hardoy and Houssay[17] proved, by experiments and clinical observations, the value of giving 1 or 2 mg. of epinephrine by parenteral administration in the Adams-Stokes syndrome with auriculoventricular block.

In 1921, Guglielmeti, Arrillaga, and Waldorp[18] showed the effect of quinidine on the heart by experiments on dogs. After a brief phase of stimulation, with increased heart rate, a second phase of depression followed, with decreased heart rate, and lessening of the excitability of the myocardium set in, preventing or abolishing experimental fibrillation of the auricles.

In 1924, Padilla[19] published a book on electrocardiography which was epoch-making in South America. Completely illustrated by his own

cases, it was an exhaustive and sound study on this important method of examination, which was quite unknown to us at that time.

Since 1928, Padilla and Cossio[20] have used quinidine sulfate intravenously in doses of 0.50 to 1.5 Gm. in a 5 per cent solution without harming their patients. This has been given to patients with paroxysmal tachycardia of ventricular or supraventricular origin, paroxysmal auricular fibrillation, and flutter; good results have been obtained even in cases in which this medication had been ineffective by mouth.

In 1929, Padilla and Cossio[21] made an exhaustive clinical and anatomic study of coronary arterial occlusion, in which they pointed out the importance of alterations in auriculoventricular and ventricular conduction, and of ventricular tachycardia in cases of infarction of the interventricular septum. In addition, they demonstrated for the first time the absence of the coronary S-T segment and of the coronary T wave in myocardial infarction with bundle branch block. Battro,[22] almost at the same time, made similar studies on coronary occlusion, and, some years later, Martinez[23] did the same.

In 1931, Martini and Joselevich[24] made an extensive clinical and anatomic study of the right ventricular failure which is caused by displacement of the interventricular septum (syndrome of Bernheim). They emphasized that the absence of lung congestion is a differential point; such congestion is characteristic of right ventricular failure secondary to left ventricular failure, which is always accompanied by pulmonary congestion of various degrees.

From 1931 until the present time, the graphic registration of heart sounds has been the object of special attention.

Braun Menéndez and Orías[25] have recorded the third physiologic heart sound in 42 per cent of 100 medical students, and the presystolic auricular sound in 15 per cent.

With my collaborators[26] I have identified a systolic and a protodiastolic sound in auriculoventricular block. The systolic sound is present when auricular contraction coincides with the middle of ventricular systole, and the protodiastolic sound occurs when auricular contraction coincides with rapid ventricular inflow, producing the summation phenomenon.

We[27] have given evidence of the alternation of heart sounds in cases of pulsus alternans. The alternation of the first sound and of the gallop rhythm is always concordant, whereas the alternation of the second sound may be concordant or discordant in such a way that the heart beat which produces the larger pulse wave has a loud first sound, pronounced gallop rhythm, and a loud or a faint second sound. I[28] have proved that often there is a third, protodiastolic sound in active rheumatic heart disease with mitral regurgitation, and also that the functional mitral murmur of rheumatic carditis occurs only in the early and middle phases of ventricular systole.

Gonzalez Sabathié[29] proved that, when there is physiologic reduplication of the second heart sound, the closure of the aortic valve precedes that of the pulmonary valve, which is contrary to all classical medical knowledge.

I[30] have shown that, with auriculoventricular nodal rhythm, the first heart sound is louder and reduplicated. This enables us to distinguish paroxysmal tachycardia of auriculoventricular nodal origin.

In 1934, Gonzalez Sabathié[31] called our attention to engorgement of the left external jugular vein as a sign of lengthening and widening of the aortic arch, with pressure on the left innominate vein.

In 1935, Moia[32] stated for the first time that the T wave of the precordial lead in normal children can be negative.

In 1937, I[33] called attention to, and named, the "bronchial dance"; this curious phenomenon, a to-and-fro movement of the bronchi on the right side, is easily seen on the fluoroscopic screen in the presence of unusual enlargement of the left auricle, with mitral regurgitation.

Also in 1937, Battro, Braun Menéndez, and Orías[34] showed that electrocardiographic patterns of bundle branch block are not always found with abnormal asynchronism in ventricular contraction.

In 1939, Enquin and Aguirre[35] were able to visualize the whole left auricle and all of the thoracic aorta by ultrapenetrating radiography, giving evidence of its usefulness in the diagnosis of heart disease.

In 1940, Arana and Kreutzer,[36] in a study of 600 children with diphtheria, found that the electrocardiographic changes are sometimes reversible, and, at other times, irreversible, which should be remembered in order to avoid a mistake in diagnosis.

In 1941, Vedoya and Gonzalez Videla[37] differentiated two types of sinoauricular block: one with occasional dropped beats and progressive lengthening of sinoauricular conduction, with heart beats in groups similar to the Wenckebach periods of auriculoventricular block; and the other, with occasional dropped beats but without the progressive lengthening of sinoauricular conduction.

Also in 1941, Cossio, del Castillo, de la Balze, and Reforzo[38] demonstrated reversible heart enlargement in cases of nontoxic goiter after thyroidectomy. This enlargement is apparently due to overstrain of the right ventricle caused by an arteriovenous fistula in the thyroid gland and the neighboring vascular bed.

Finally, since 1937, arterial hypertension caused by clamping the renal arteries of dogs has been the subject of a great deal of study.

In 1937, Houssay and Fasciolo[39] gave a clear demonstration that the ischemic kidney of hypertensive dogs liberates a pressor substance into the blood. Grafting such kidneys into the necks of recently nephrectomized dogs caused a rise in the blood pressure of the recipient dog. Later, Houssay and Taquini[40] showed that the citrated plasma of the

venous blood of ischemic kidneys produces marked vasoconstriction in the Läwen-Trendelenburg preparation of the toad.

In 1939, Braun Menéndez and Fasciolo[41] showed that acute ischemia of the kidneys produced the same effects, and, with Leloir and Muñoz,[42] discovered in this blood the substance, hypertensin, that is responsible for the pressor and vasoconstrictor properties of the venous blood of ischemic kidneys. It was found that this substance is formed by the enzymatic action of renin on a blood globulin called hypertensinogen. Another enzyme, hypertensinase, which is present in blood and tissues, destroys hypertensin. The ischemic kidneys secrete renin into the blood, and hypertensin is formed subsequently in the blood by the action of renin on hypertensinogen (Leloir, Muñoz, Braun Menéndez, and Fasciolo[43]). Renin has been found in the renal venous blood and in the general blood of hypertensive dogs (Dell 'Oro and Braun Menéndez[44]). The experiments of Huidobro and Braun Menéndez[45] have shown that renin is secreted, even by normal kidneys, whenever the blood pressure falls. The kidney thus seems to play its part in the normal regulation of arterial blood pressure.

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# PATENCY OF THE DUCTUS ARTERIOSUS IN ADULTS

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MINNEAPOLIS, MINN.

THE first successful ligation of a patent ductus arteriosus was reported by Gross and Hubbard,[30] in 1939. Since that date, numerous additional successes, and some failures, have stimulated much interest in the subject. Gross[31] (1941) has now operated on thirty patients with only two fatalities. The record of Jones[42] is almost as impressive: twenty-six operations with two failures. We now have records on 134 operations to ligate the ductus; nearly half of these have not been reported except by personal correspondence to the authors. The analysis of those operations will be reported elsewhere (Am. J. M. Sc., in press).

Patency of the ductus arteriosus is apparently much more common than was previously believed. We have personally studied, with some care, fifty-one patients with this condition in the Minneapolis and St. Paul area. Jones, Dolley, and Bullock[13] have seen about sixty-five cases in the Los Angeles area. Rough calculation would suggest that there are at least 20,000 persons with a patent ductus arteriosus in the United States at the present time. There is clearly a need for careful consideration as to what should be done with these people. Apart from consideration of the immediate results of operation, there is the question as to what eventually happens to persons with patency of the ductus arteriosus in the ordinary course of events. Evidence is obtained on this point from a consideration of our own patients, many of whom have been followed for years (several for eighteen years each). In addition, there are the scattered reports in the literature which have never been satisfactorily collected and analyzed. This paper is a report on patency of the ductus in adults; adults are defined as persons 17 years of age and older. Further, we shall confine ourselves primarily to cases in which autopsies were performed. For this analysis we have clinical and post-mortem records of sixty-seven patients in the literature and four patients from our own series. Of these, sixty-one patients had no other important abnormalities and may be considered typical.

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Since this paper was written, one of our patients who had been under observation for ten years developed subacute bacterial endarteritis and was dead within three months. We were not informed of her condition until after her death. She was a sixteen-year-old girl who was apparently in good health until the endarteritis developed. Physical examination revealed typical signs of patency of the ductus arteriosus. The heart was of normal size. She had had no symptoms. Surgical treatment had been advised previously, but was refused. Post-mortem examination revealed a widely patent ductus, with superimposed bacterial endarteritis. The heart weighed 275 grams. Five additional patients have been operated upon in the past year by Dr. Owen Wangensteen, all with complete success.

*Reports From the Literature.*—The first case of typical patency of the ductus arteriosus in an adult, with clinical and post-mortem observations, was reported by Chevers[17] in 1845. The patient, an adult woman, was said to have died of tuberculosis, but, from the meager history and post-mortem report, it appears possible that death may actually have been caused by subacute bacterial endarteritis.

Brief notes on the cases from the literature are given in Appendix A to this article. Before considering the salient characteristics of these cases, we shall report the adult patients of our own who came to autopsy.

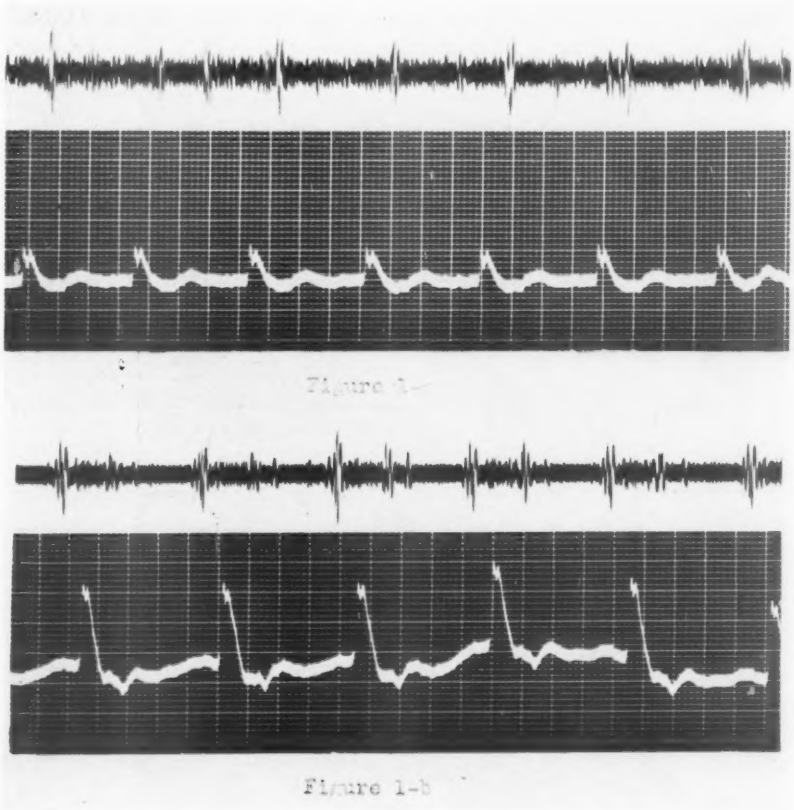

Fig. 1*a*.—Stethocardiogram and simultaneous pulse wave record on patient No. 1, before operation. Stethophone in second left intercostal space, pulse recorder on right brachial artery.

Fig. 1*b*.—Same as Fig. 1*a*, but four days after operation. Note that same amplification was used as in Fig. 1*a*.

## REPORT OF AUTHORS' CASES

In a total of 51 cases, we have had 4 adult patients who came to autopsy. These are as follows:

CASE 1.—This 18-year-old man had been studied repeatedly over a period of 6 years; the diagnosis of heart disease had been made at the age of 2 years. His

general health had been fairly good, but there was an increasing complaint of exertional dyspnea, cough, and inability to do physical work. At the same time there was a gradual increase in the blood pressure, the size of the heart shadow, and the density of the hilar shadows. Surgical closure of the ductus was recommended. At operation the posterior junction of the ductus and pulmonary artery was ruptured, and the bleeding could be controlled only by clamps. The patient died on the ninth postoperative day.

*Physical Examination Before Operation.*—The patient was well developed and nourished, with no cyanosis, clubbing, or signs of cardiac failure. There was a marked thrill over the pulmonic area, and, in this region, there was a loud murmur which was typical of patency of the ductus arteriosus; the murmur was transmitted upward, to the left, and to the back. The heart was moderately enlarged, chiefly to the left. The apical impulse was visible in the sixth left intercostal space. The pulmonary arc was considerably enlarged. The blood pressure was 144/40, and the pulse rate, 88. There were a Corrigan pulse in the neck and a capillary pulse in the finger tips.

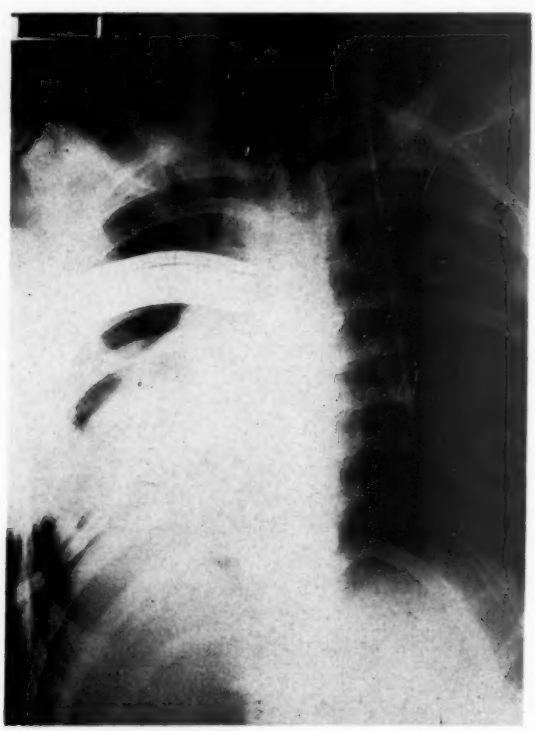

Fig. 2.—Roentgenogram of chest of patient No. 1 after operation. Note clamps on ductus and adjacent portion of pulmonary artery.

*Special Examinations.*—On 3 occasions, in the basal resting state, the blood pressure in the right arm was 152/40/0; in the left arm, 146/60/0; in the right leg, 204/120/80/0; in the left leg, 190/60/0; the pulse rate was 84. The basal metabolic rate was +1 per cent, -2 per cent. Total systolic heart volume (roentgenkymograph) was 980 c.c. Total body surface, 1.75 $M^2$. Net cardiac output (acetylene), 3.79 L./min., stroke, 43.8 c.c. Gross cardiac output (roentgenkymogram), 7.56 L./min., stroke, 90 c.c. Flow through ductus, about 50 per cent of output of left ventricle.

*Autopsy* (abstract).—Body length, 179 cm.; weight, 145 pounds. Moderate cyanosis of nailbeds; no jaundice. Left lung collapsed, left pleural cavity filled with fibrinoplastic material with numerous pockets of clear serous fluid. There were about 50 c.c. of this fluid in the right pleural cavity.

About 150 c.c. of slightly bloodtinged purulent fluid were found in the pericardial cavity. A fine, plastic, readily broken exudate united the pericardium with the anterior surface of the left ventricle. *Streptococcus viridans* was cultured from the pericardial material. There were five hysterectomy clamps in the region of the ductus arteriosus.

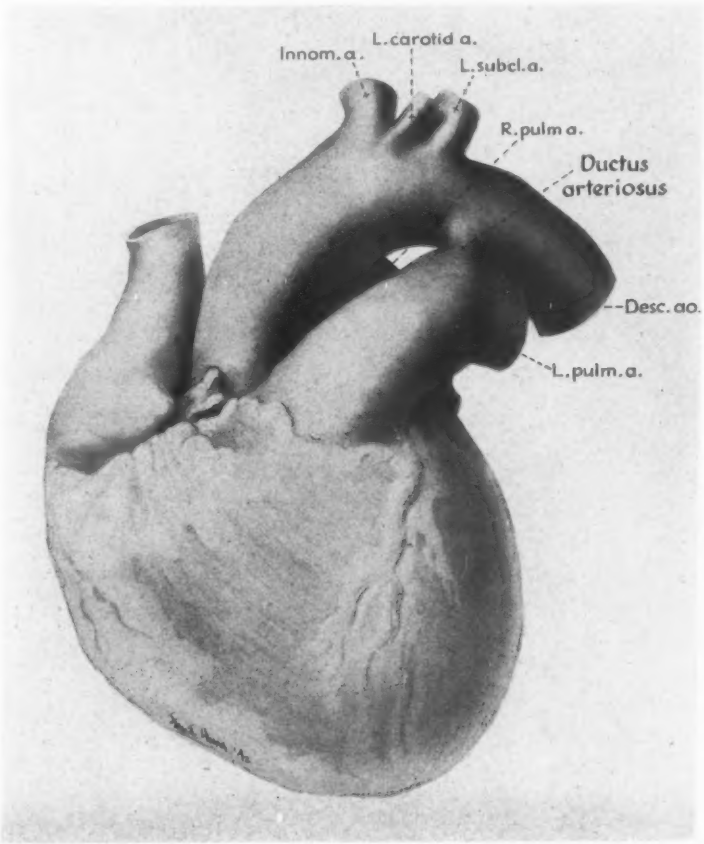


Fig. 3.—Anterior view of the heart and great vessels of patient No. 2.

Heart weight, 650 grams; generalized hypertrophy, more on right than the left side. Marked right-sided cardiac dilatation. All valves and chambers normal; marked hypertrophy of the papillary muscles of tricuspid and mitral valves. Length of the ductus arteriosus, 5 mm. on the cardiac side, and 2 or 3 mm. on the lateral side. The aortic orifice was about 8 mm. in diameter, the pulmonary orifice, 3 mm. Minimal atherosclerosis in the aorta, none in the pulmonary artery.

The left lung was completely atelectatic, with no emboli, infarcts, or abscesses. The upper lobe of the right lung showed moderate edema; most of the lower right lobe was atelectatic. There was a sterile abscess, 2 cm. in diameter, in the head of the pancreas. There was nothing else of importance.

*Diagnoses.*—(1) Patency of the ductus arteriosus, (2) surgical closure of the ductus, (3) atelectasis of left lung, (4) slight fibrinous pericarditis, and (5) fat necrosis of the pancreas.

*Comment.*—The attempted ligation of the ductus was justified in view of the evidence of decreasing tolerance to the condition. The shortness of the ductus on one side presented a difficult surgical condition. After the ductus was clamped off, the patient's condition was fair, and the blood pressure was 125/80. Nine days later, at death, there were no signs of union of the compressed inner surfaces of the ductus.

CASE 2.—This 58-year-old man was admitted to the hospital with complaints of stomach trouble for many years, and weakness, with gastrointestinal symptoms, for 18 months. A diagnosis of carcinoma of the stomach was followed by subtotal gastrectomy. Death occurred 38 days later, preceded by pulmonary edema and hydropneumothorax.

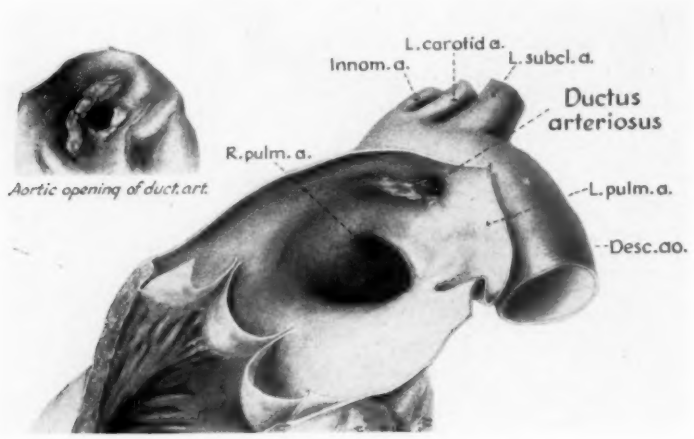


Fig. 4.—Opened aorta and pulmonary artery of patient No. 2. Note normal pulmonary endothelium, with atheromatous patch at the orifice of the ductus.

*History.*—Aside from the long history of stomach trouble and a transurethral prostatic resection 6 years before admission, this patient had always been reasonably well and able to earn a living at fairly hard work. Twenty years earlier he had been told he had heart trouble but had suffered no symptoms except moderate exertional dyspnea. A diagnosis of patency of the ductus arteriosus was made prior to gastrectomy.

*Physical Examination.*—There was a machinery murmur, typical of patency of the ductus arteriosus, with a slight thrill, over the pulmonic area. The heart was enlarged to the left; the pulmonary artery was prominent; the aorta was somewhat tortuous and calcification was present in the arch. There were no signs of cardiac failure. The blood pressure was 126/56.

*Special Examination.*—The blood pressure in the right arm was 130/58; in the left arm, 154/58; in the right leg, 160/60; and in the left leg, 160/60; pulse rate, 94. Total body surface, 1.70 $M^2$. Basal metabolic rate, +35 per cent; +22 per cent. Total systolic heart volume (roentgenkymogram), 660 c.c. Gross cardiac output (roentgenkymogram), 5.76 L./min.; stroke, 62 c.c. Flow through ductus, about 30 per cent of total left ventricular output.

*Autopsy (Abstract).*—Body length, 180 cm.; weight, 140 pounds. No jaundice or cyanosis; slight edema of the ankles. Atelectasis and crepitation of the lungs, three large decubital ulcers on the back, marked dilatation of the large bowel.

The heart (and great vessels) weighed 550 grams, and both ventricles were hypertrophied. The ductus arteriosus was very short, but widely patent. The chambers, myocardium, and valves were normal. The pulmonary conus was dilated; the intima of the pulmonary artery was smooth and normal except for thickening in the region of the orifice of the ductus. The aortic wall showed moderate calcification in this region but was otherwise normal. Atherosclerotic changes were generally absent in the great vessels and were minimal in the coronaries.

The liver weighed 1,850 grams, and showed pigmentation, congestion, and central atrophy.

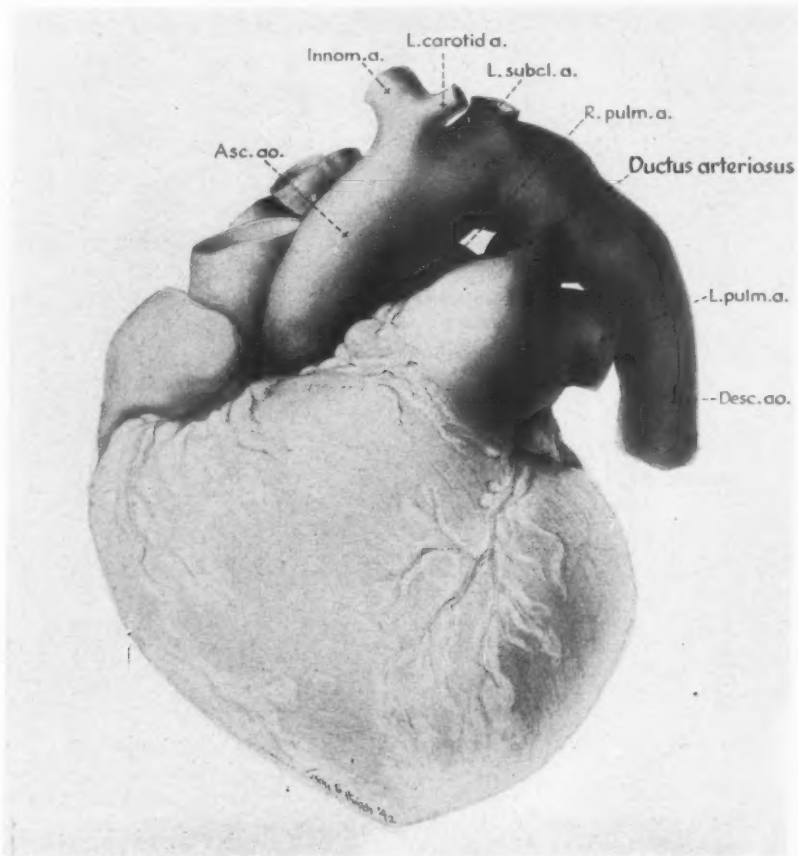


Fig. 5.—Anterior view of the heart and great vessels of patient No. 3.

*Diagnoses (Abstract).*—(1) Carcinoma of the stomach, removed surgically, (2) hydrothorax, (3) pulmonary edema, (4) paralytic ileus (colon), (5) patency of the ductus arteriosus, (6) cardiac hypertrophy and dilatation, and (7) chronic passive congestion of liver.

*Comment.*—This patient had suffered remarkably little disability from patency of his ductus arteriosus throughout a life of moderately hard physical labor. There is no reason to believe that his death was related to the cardiac condition. Ligation of the ductus would have been difficult because of its shortness. The normal condition of the intima of the pulmonary artery was notable.

CASE 3.—This 46-year-old woman was admitted to the hospital July 29, 1941, and died August 7. Her entering complaints were dyspnea, nausea and vomiting, anorexia, and pains in the feet, all of which had gradually increased in severity for several weeks.

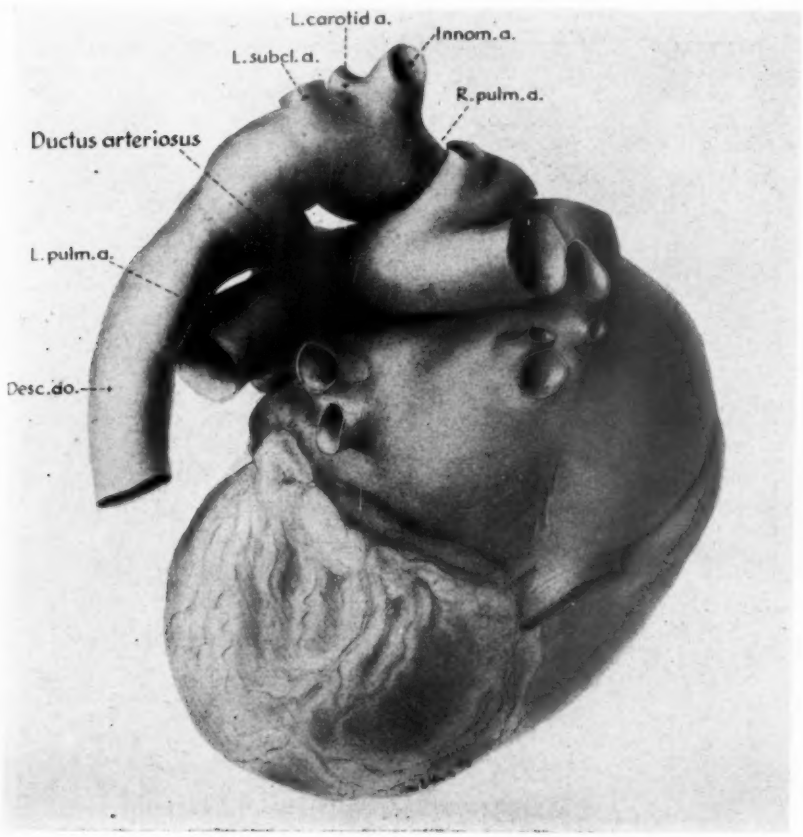


Fig. 6.—Posterior view of the heart and great vessels of patient No. 3.

*History.*—Since the age of 5 years, she had known that she had heart trouble, and had always led a somewhat sheltered but otherwise normal life. Her general medical and family history were unimportant.

*Physical Examination.*—She was well developed and moderately obese. There were generalized anasarca, moderate ascites, and moderate cyanosis. The heart was greatly enlarged to the right and left, and the contour was that of congenital or mitral disease. The pulmonary artery was markedly enlarged, and the hilar shadows much enlarged. The heart sounds were rapid and regular, with no murmurs; there were râles in both bases. There was no fever or petechiae. The blood pressure was 142/40.

*Urinalysis.*—Sp. gr., 1,030; albumin, +++; occasional bacteria and 6 to 8 leucocytes per microscopic field.

*Diagnosis.*—Congestive heart failure and congenital heart disease (interauricular septal defect?).

*Course.*—The patient grew worse rapidly and died of heart failure.

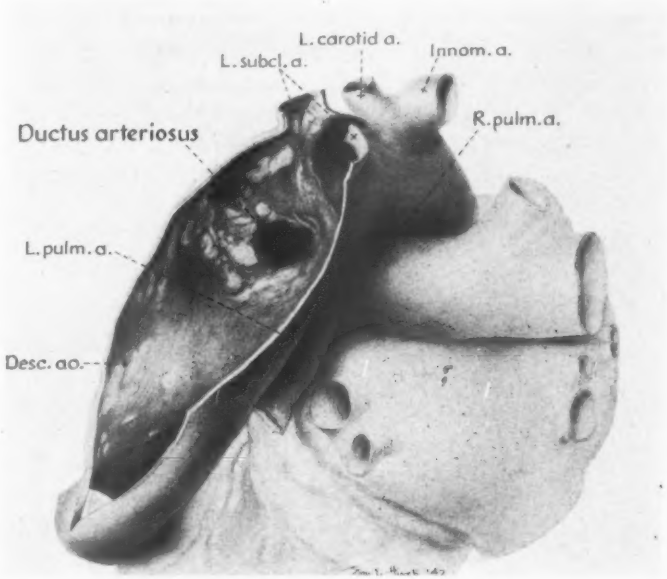


Fig. 7.—Opened aorta of patient No. 3. Note numerous atheromata and slight fold at orifice of the ductus.

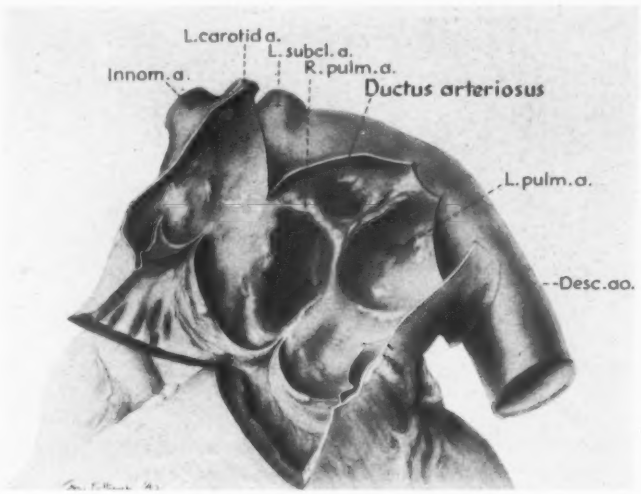


Fig. 8.—Opened pulmonary artery of patient No. 3. Note atheromata.

*Autopsy (Abstract).*—No edema, cyanosis, or jaundice. Weight, 125 pounds; length, 157.5 cm. The liver extended 6 cm. below the xiphoid and 2 cm. below the costal margin.

The heart weighed 700 Gm.; it showed marked right ventricular hypertrophy and some left ventricular hypertrophy. The ductus arteriosus was patent and was about 2 cm. long and 1.5 cm. wide. The pulmonary conus and the branches of the pulmonary artery were markedly enlarged. All of the valves were normal, and there were no septal defects. There was minimal atherosclerosis of the coronary arteries; the coronary orifices were normal. There was marked intimal atherosclerosis of the root of the aorta, the ductus arteriosus, and the pulmonary artery.

The liver weighed 1,425 Gm. and showed moderate congestion.

Microscopic examination revealed marked arteriosclerosis of all branches of the pulmonary artery. There was a large ante-mortem clot in the right main branch of the pulmonary artery.

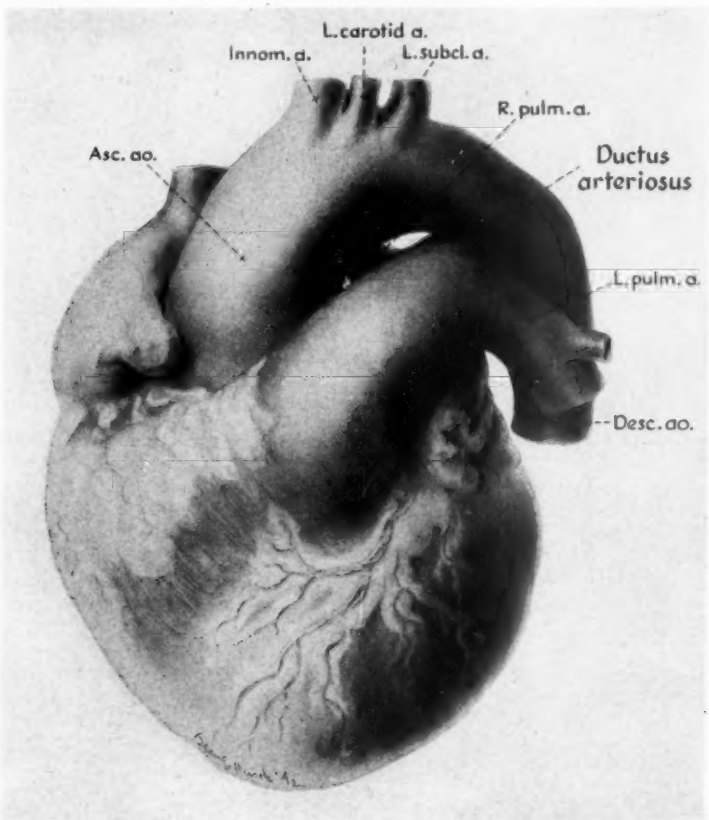


Fig. 9.—Anterior view of heart and great vessels of patient No. 4.

*Diagnoses.*—(1) Patency of the ductus arteriosus, (2) right ventricular hypertrophy and dilatation, (3) pulmonary thrombosis or embolism, (4) pulmonary arteriosclerosis, and (5) mild chronic passive congestion of the liver.

*Comment.*—The large patency of the ductus arteriosus allowed 46 years of moderately normal life but ultimately led to right ventricular failure. The diagnosis was impossible because there was no murmur. It is possible that the murmur was audible before the onset of failure. Anatomically, there appeared to be no reason why ligation could not have been performed successfully.

CASE 4.—This 53-year-old woman was first admitted to the hospital September 2, 1941, and died February 5, 1942. Her entering complaints were headaches, nausea, vomiting, and fever, beginning about August 27, 1941.

*History.*—She had been told her heart disease was discovered before she was one year of age. A definite diagnosis of congenital heart disease was made at the age of 12 years. She had never been incapacitated but was always forced to restrict her physical activity. At no time did she have complaints suggesting cardiac failure. At the age of 19 she had received digitalis for a time (reason unknown).

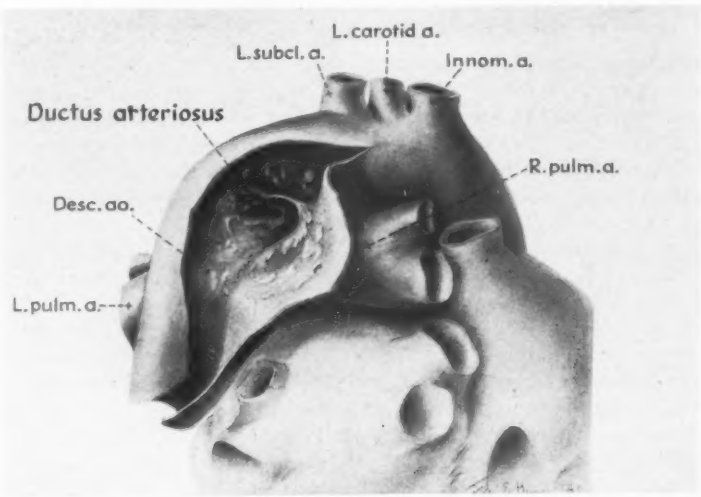


Fig. 10.—Opened aorta of patient No. 4. Note atheromata and fold at orifice of ductus.

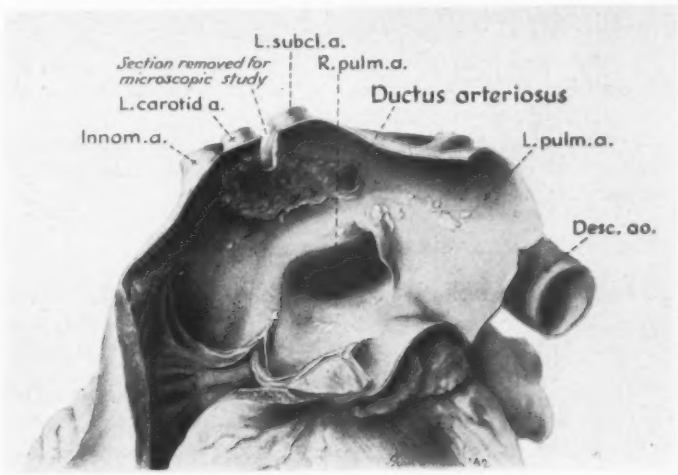


Fig. 11.—Opened pulmonary artery of patient No. 4. Note heavy patch of atheromata.

*Physical Examination.*—She was well developed and nourished. There was no cyanosis or clubbing. A systolic thrill was palpable in the second left intercostal space, and a machinery murmur, typical of patency of the ductus arteriosus, was heard over this region. The systolic phase of the murmur was transmitted upwards and to

the back. She had a Corrigan pulse and a capillary pulse in the finger tips. There were râles in both bases. Both the liver and spleen were palpable, but not tender. There were no petechiae. The blood pressure in the arm was 140/65, and in the leg, 170/96. Her temperature ranged from 98° to 103° F. *Streptococcus viridans* was recovered from the blood culture in 48 hours. The hemoglobin was 74 to 80 per cent.

The heart was enlarged to the left and right. There were marked enlargement of the pulmonary artery and increased shadows of hilar vessels.

*Urinalysis.*—Trace of albumin; sp. gr., 1.002 to 1.018; no casts or erythrocytes; 1 to 8 leucocytes.

*Diagnosis.*—Patency of the ductus arteriosus, with superimposed subacute bacterial endarteritis.

*Course.*—Several courses of sulfathiazole, sulfanilamide, and sulfadiazine were ineffective. Repeated blood transfusions increased the hemoglobin level from 55 per cent to 89 per cent. The temperature was normal during the last three weeks in hospital. Arrangements were made to attempt to ligate the ductus, but the patient expired after twenty minutes of anesthesia (cyclopropane intratracheally) before the operation was started.

*Autopsy (Abstract).*—No edema, petechiae, or jaundice; marked cyanosis. Body length 158 cm.; weight, 110 pounds. The liver was 11 cm. below the xiphoid process in the midline, but even with the costal margins on the right and left.

The heart weighed 490 Gm.; it showed slight hypertrophy of the right ventricle and more marked hypertrophy of the left ventricle. The aortic, pulmonary, and tricuspid valves were normal. The mitral valve showed some old thickening and two recent vegetations on the medial leaflet. The coronary orifices were normal. The ductus arteriosus was patent and measured 12 mm. in external diameter; its smallest bore was about 3 mm. in the contracted specimen. Vegetations and several atheromata were present in the pulmonary artery. There was an infarct, 1 cm. in diameter, in the upper lobe of the left lung, and another, 3 cm. in diameter, in the left lower lobe. The spleen was firm, deep red in section, and weighed 520 grams. The liver showed long-standing passive congestion, and weighed 1,720 grams.

*Diagnoses.*—(1) Subacute bacterial endarteritis, (2) patency of the ductus arteriosus, (3) infarcts of lung, (4) ascites, (5) chronic passive congestion of liver, (6) septic splenitis, (7) uterine myomata, (8) left ventricular hypertrophy, and (9) dilatation of left auricle and ventricle.

*Comment.*—The correct diagnosis was not made by the original attending physician. The physical condition of the patient at this time, some months after the onset of the infection, made her a poor operative risk.

### ANALYSIS OF 60 CASES IN ADULTS

In an analysis of pathologic changes and cause of death it is not justifiable to include our own Case 1, so that we have in our series a total of 60 adults with typical, simple patency of the ductus. There were 14 men and 46 women; 76.7 per cent were women. The preponderance of females with patency of the ductus arteriosus is, if anything, more marked in adults than it is in series of all ages and of children previously summarized in the literature. For example, in Maude Abbott's[2] series of 97 cases in which the average age was 21.2 years at death, the females comprised 63 per cent of the total.

The average age at death of the 14 men in the present series was 38.9 years; that of the 46 women was 35.5 years. The oldest man died at 58, and the oldest woman, at 66 years. We can estimate the reduction in

length of life by comparison with the average life expectancy of the general population. Properly, this comparison should be made for each individual in this series, using the life tables for the year of death and for the country of residence. Such exact comparison is impossible, but a reasonable estimate can be made. Since the life expectancy of adults is not greatly different in the United States, England, and the northern European countries in which the rest of the patients resided, we can refer to the United States Life Tables with no great error. Further, the life expectancy of adults has shown a fairly constant, slow increase in these countries for many years. The chronological mid-point of the present series is close to 1910; that is, roughly, half of the patients died previous to that time. Accordingly, it appears desirable to use the tables for that year.

By this means we can say that the presence of patency of the ductus arteriosus in the persons in the present series coincided with an average reduction in life expectancy of about 23 years in the men and 28 years in the women. Expressed in another way, we can say that these people, who were alive at the age of 17, had a life expectancy which averaged about half that of the population as a whole. The interpretation of these figures will be treated further in the Discussion.

The cause of death in these cases is shown in Table I. Subacute bacterial endarteritis accounted for more than 40 per cent, and congestive heart failure for nearly 30 per cent. The two deaths from rupture of aneurysms of the pulmonary artery (Nos. 26 and 41) also must surely be ascribed to the condition of the ductus. Roughly, 4 out of 5 of these persons eventually succumbed to the effects of patency of the ductus. This is the more striking when we note that the majority of these persons lived many years, during which they were apparently well adjusted to the defect.

TABLE I

CAUSE OF DEATH IN 60 ADULTS WITH PATENCY OF THE DUCTUS ARTERIOSUS

| NO. | % | CAUSE | NO. | % | CAUSE |
|---|---|---|---|---|---|
| 25 | 41.7 | Subacute bact. endart. | 2 | 3.3 | Prob. subacute bact. endart. |
| 17 | 28.3 | Cong. failure | 3 | 5 | Tuberculosis |
| 2 | 3.3 | Rupt. pulm. aneurysm | 2 | 3.3 | Rupt. aortic aneurysm |
| 2 | 3.3 | Cerebrovascular | 1 | 1.7 | Pneumonia |
| 1 | 1.7 | Ca. of stomach | 1 | 1.7 | Yellow atrophy |
| 1 | 1.7 | Suicide | 3 | 5 | Questionable |

It is generally stated that hypertrophy of the right side of the heart is characteristic of patency of the ductus arteriosus, and this is said to be the result of increased pressure in the pulmonary artery. Table II summarizes the observations in the present series. It is clear that hypertrophy of the right side of the heart is frequent, but, in many cases both sides were equally hypertrophied, and cases of predominantly left-sided heart hypertrophy are not rare. In some cases neither side was hypertrophied.

TABLE II

THE SIZE OF THE HEART IN 60 ADULTS WITH SIMPLE PATENCY OF THE DUCTUS ARTERIOSUS

| ENLARGEMENT | PREDOM. RIGHT | PREDOM. LEFT. | BOTH SIDES |
|---|---|---|---|
| Great | 11 | 2 | 4 |
| Moderate | 8 | 4 | 10 |
| Slight | 2 | 2 | 3 |
| No enlargement | | 5 cases | |
| Not stated | | 9 cases | |

Dilatation of the pulmonary artery is, of course, frequently associated with patency of the ductus arteriosus. It is not uncommon, however, to find that such dilatation is not demonstrable roentgenologically. We believe that this dilatation is, in fact, nearly always present in adults, for it occurred in the majority of the patients in the present series. In ten cases, actual aneurysms of the pulmonary artery were present. There may be some argument as to the definition of "aneurysm"; certainly many fusiform dilatations of the pulmonary artery do not merit the term. When the dilatation is profound and well circumscribed, however, with degenerative changes in the walls, such an appellation seems justified. We have noted that spontaneous rupture of such aneurysms resulted in two deaths.

The presence of atheromata and calcareous plaques in the pulmonary artery has been noted many times before and was prominent in all of our cases (cf. Figs. 4, 8, 11). This is so frequent that it is the rule in adults. Exceptions occur, however, notably the 65-year-old patient of White.[91] The fact that these atheromata and plaques occur with almost equal frequency in the aortas of these patients has not been stressed previously.

The length of the ductus is of interest in view of the present possibilities of ligation. In general, the ductus is short in adults, and cases in which it is a centimeter or more in length are rather rare (Appendix A, Nos. 24, 27, 40, 46, 52, 53). Cases are not uncommon in which the ductus is extremely short, or even reduced to a mere fistula-like opening between the aorta and pulmonary artery. In the present series, cases of this type, representing very difficult or frankly inoperable conditions, comprised 17 per cent of the total (10 out of 60 cases, cf. Appendix A, cases 2, 4, 10, 18, 19, 25, 33, 37, 48, 55). Lenz[53] reported a case of this type in an adult, with calcification of the point of junction of the aorta and pulmonary artery; we have been unable to obtain the paper in which this is reported, so that we have not included the case in the present series. The frequency of this condition appears to be considerably greater in adults than in infants and children, although it may occur in very young infants (Lediberder[52]).

It would be of much interest to compare the size of the lumen of the ductus with the severity of the cardiac disability and cause of death in these cases, but this is not possible because of the absence of quanti-

tative data on the bore of the ductus. Even if post-mortem measurements were available, accurate comparison would be difficult because of the fact that the size of the bore in the post-mortem contracted specimen may be quite different from what it was in life, when the vessel was distended with blood under arterial pressure. We might expect that congestive failure would be more frequent when the communication is very large, but no real proof of this exists.

The diagnostic signs in the present series clearly pointed to patency of the ductus arteriosus in most of the cases, and, except in the earlier cases, the diagnosis was made correctly in the majority of instances. In several instances, however, the diagnosis could not be made because there was no murmur. This was true in the case of Duroziez[22] and in one of our own cases (Case 1). Foulis[25] found that the murmur in his case disappeared entirely twenty-six days before death. All of these three patients died of congestive failure. The history in Motzfeldt's[61] first case (Appendix A, No. 31) was incomplete, but the diagnosis was not made, and it is explicitly stated that there was no mention of any murmur. In addition, in two instances only faint atypical murmurs were heard (Appendix A, Nos. 36, 39).

Sternberg[75] stated that there is always a characteristic shape and form of the patent ductus arteriosus, in that the opening of the ductus into the aorta is funnel-shaped, and at the pulmonary orifice there is some sign of a membrane or ridge. Jores[43] agreed that this condition is very frequent, but also recognized several other types: (1) Extreme shortening, (2) aneurysmal ductus, and (3) cylindrical ductus. In the present series we have already noted the extremely short ductus type. Cases in which the aortic orifice of the ductus was considerably larger than the pulmonary orifice are frequent (Appendix A, Nos. 12, 17, 22, 23, 27, 29, 30, 36, 37, 39, 46, 53). In at least one case, however, the pulmonary orifice was larger than the aortic orifice (Appendix A, No. 24). The membrane or ridge referred to by Sternberg has been extensively discussed since Strassmann's[77] publication of his theory of closure. In adults, at least, such a condition is occasionally seen (Wells;[90] cf. Figs. 7 and 10), but does not appear to have any important significance; a fold of the wall may occur at both orifices,[54] but tends to occur at the aortic orifice because of the acute angle of insertion of the ductus into the aorta (cf. Roeder[68]).

### COMPLICATED AND ATYPICAL PATENCY OF THE DUCTUS

Patency of the ductus arteriosus is peculiar among congenital defects in that it so frequently occurs without associated abnormalities. In Maude Abbott's[2] series of 1,000 cases of congenital heart disease at all ages, simple patency of the ductus occurred in 92 instances, and, in 150 instances, patency of the ductus complicated other defects. Most of the latter patients died in infancy or at an early age, and we suspect that

the relative proportion of simple patency to complicated conditions is considerably greater in adults.

We have collected data on ten adults, with post-mortem observations, in whom patency of the ductus was the most prominent abnormality, but in whom the patency was not typical or some other defect was present. These are listed, with brief notes, in Appendix B of this paper. This list could be easily enlarged by including cases of transposition of the great vessels, septal defects, pulmonary atresia, and so on, but these have been excluded in the belief that it is not a concern of this inquiry to examine situations in which patency of the ductus is secondary to other defects.

It is of interest to note that, in this series, nine of ten of the patients were men. In four instances there was associated coaretation of the aorta (Appendix B, Nos. 1, 3, 8, and 9). In three instances the ductus was aneurysmal and filled with an organized or partly organized clot (Nos. 2, 6, 10). The experience of Graham[28] is illuminating. He tried to remove a mediastinal tumor and discovered, post mortem, that the tumor was in reality an aneurysm of the ductus arteriosus. Shortly afterward he encountered a similar case surgically, but was able to retreat before it was too late.

The two cases reported by Wagener[86] are curiosities. In each instance the ductus was open to the pulmonary artery, but the orifice of the latter was closed by a firm membrane. This membrane was pierced by a single pinhole in one patient and by two such pinholes in the other. As one would expect, there was no cardiac disability in either case.

## DISCUSSION

The application of autopsy results to clinical prognostication is always difficult because of the question of selection of cases. This was recognized by Bullock, Jones, and Dolley,[14] who included many of the present cases in their discussion of cause of death in patency of the ductus arteriosus. Specifically, the chief possibilities that the present series is not representative seem to be: (1) Remarkable and peculiar cases tend to be reported more frequently than typical cases. (2) Patency of the ductus may be unrecognized and therefore unreported, when patients die of noncardiac conditions.

With regard to the first point, it will be agreed that remarkable cases are more frequently reported. Patency of the ductus in the adult is and has been generally considered a rather remarkable abnormality, regardless of the cause of death. If anything, we should expect that authors would compete to report the oldest patients and those cases in which a marked lesion was well tolerated. In other words, we might believe that the present series would include the oldest patients, as well as those cases in which the cardiac lesion had no relation to death. If this were true, the analysis of the present series would underestimate the disabling and lethal effect of patency of the ductus.

It is certain that many autopsies on persons with patency of the ductus fail to disclose the lesion because of the frequent use of the method of removing the heart in which the aorta and pulmonary artery are severed proximal to the ductus. This error would tend to be more frequent in cases of noncardiac death, and hence there would be a tendency to overestimate the disabling and lethal effect of patency of the ductus.

One important question may be asked: Where are the adult, living patients with patency of the ductus? In any large city it is possible to find a few cases of patency of the ductus, but, in our experience, these are almost always in children. Further, it should be emphasized that, when we are dealing with adults, at least, there is no reason why persons with patency of the ductus who die in the second and third decades should be discovered more readily or reported more often than those who die later.

Many of the patients in our own clinical series have been observed for years, and fully half of them for periods of four to eighteen years. With the exception of the patient who died after operation, only one of them exhibited any very marked change of status during all this time. (In Cases 3 and 4 in the series presented in this paper the patients were not seen prior to the beginning of the final illness.) In general, they live fairly normal lives, go to school, or earn a living. One patient, a man of 35 years, is a playground supervisor. Another patient, a woman of 19 years, wishes to study physical education in the University. A third patient, a man of 28 years, has been rejected by the Army but works steadily at heavy manual work and has remarkable muscular development. Among the adults, only one, a prostitute of 31 years, shows signs of impending, serious, cardiac embarrassment.

These facts could be taken as evidence that most patients with patency of the ductus arteriosus need not have the ductus ligated. Our patients are still quite young, however, and the fact that they keep in excellent condition, even for a good many years, does not mean that they have any security against eventual subacute bacterial endarteritis or cardiac failure. It is striking in our own experience, and in the cases listed in Appendix A, that patients with patency of the ductus arteriosus do not, in general, have long and repeated periods of failure or great cardiac disability before the final illness. Almost none of them are "cardiac cripples." It is the rule that they maintain good compensation until either subacute bacterial endarteritis or cardiac failure intervenes. Very few survive once they develop failure; in this respect, these patients are in marked contrast to patients with mitral disease. Subacute bacterial endarteritis is just as fatal in cases of patency of the ductus arteriosus as in other types. There is a record of one case in which a patient with a patent ductus developed subacute bacterial endarteritis and finally recovered completely after several years;[16] the treatment in this case was entirely symptomatic.

The diagnosis of patency of the ductus arteriosus can be made with great certainty, as shown by the fact that we know of only two diagnostic errors among 134 patients who were operated upon. We should note that, in general, patients about whom there is any question of diagnosis will not be subjected to surgical exploration. Certainly we know, as was observed earlier in this paper, that anatomically typical patency of the ductus can exist with only an entirely atypical systolic murmur or even with no murmur at all. Those conditions seem to occur most frequently in the final stages of failure and may represent only a terminal abnormality of blood pressure relationships in the great vessels.

Very rarely it may happen that a murmur and other signs typical of patency of the ductus arteriosus will exist for years and then disappear, leaving the patient apparently normal. We have had two cases of this type, and several others, not very well authenticated, have been recorded in the older literature. We are discussing these apparently spontaneous closures elsewhere, but here it is enough to indicate that the phenomenon may occur, but is certainly very rare, and probably need not be considered in any practical analysis of the eventual outlook for patients with patency of the ductus.

The natural history of patency of the ductus in the adult indicates a prognosis that is good to the extent that the patient may usually expect to live a considerable number of years with relatively slight disability. On the other hand, every patient is faced with the constant threat of subacute bacterial endarteritis. Moreover, we can at best do no better than say that life will probably be short. As far as can be seen, there is no reason to place these patients on any particularly restricted regime; patients who are voluntarily quite active seem to get along as well as the patients who are constantly prevented from the slightest exertion.

The present discussion can hardly close without some statement as to the desirability of ligation of the ductus. Elsewhere we shall present an analysis of 134 operations; the salient features are low mortality and a high percentage of what seem to be complete cures. Such patients should be freed of the possibility of developing congestive failure. It is not yet certain that these patients are completely insured against subacute bacterial endarteritis. In adults, at least, it is probable that there are some atheromata in the great vessels, and these might present focal points for infection. We cannot say whether these atheromata will eventually regress. In any event, the orifices of the ductus in the aorta and the pulmonary artery will represent crypts which might afford lodging for infection. The remarkable success of Touroff, et al.,[81, 82] and Bourne, Keele, and Tubbs[10] with ligation in the presence of subacute bacterial endarteritis may be taken as an indication that it is unlikely that patients with a ligated ductus will be likely to develop subacute bacterial endarteritis in the region of the ductus.

SUMMARY

1. Brief notes are given on 57 adults, with post-mortem examinations, who had simple, typical patency of the ductus arteriosus. A few data are presented on 10 adults with atyical patency of the ductus arteriosus.

2. Case reports are presented on four adult patients, with post-mortem examinations, who had simple patency of the ductus arteriosus.

3. In simple patency of the ductus arteriosus the cause of death was subacute bacterial endarteritis in over 40 per cent of the cases; 28 per cent died of congestive failure. Death resulted from rupture of a pulmonary aneurysm in two cases (3.3 per cent).

4. After the age of 17 years, patency of the ductus arteriosus was associated with an average reduction of life expectancy of about 25 years; this is about half the life expectancy of the general population. In the majority of cases the patient's life is fairly normal while it lasts.

5. Both right- and left-sided cardiac hypertrophy occurred in these cases, but there was no enlargement in at least 10 per cent. Pulmonary aneurysms occurred in about 15 per cent. Atheromata and calcareous plaques occurred frequently, and the aorta was involved almost as often as the pulmonary artery.

6. In these adults the ductus was usually short, and, in some cases, was represented by a fistula-like communication between the aorta and pulmonary artery. Difficult or even inoperable conditions occurred in about 17 per cent of the cases. The aortic orifice is usually larger than the pulmonary orifice.

7. A correct diagnosis of patency of the ductus can generally be made without great difficulty, but in some cases the condition cannot be recognized because of the complete absence of any murmur.

8. Among adults with simple patency of the ductus arteriosus, women predominate, representing about three-fourths of the cases. In atypical patency, however, this sex ratio seems to be reversed.

9. From analysis of the available data it is concluded that an attempt at ligation of the ductus is justifiable in spite of the absence of signs of decreasing adjustment to the defect. It must be expected that, in adults, difficult or impossible operative conditions will occur frequently.

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## Appendix A

### SIMPLE PATENCY OF THE DUCTUS IN ADULTS

These are brief notes on 57 patients, reported in the literature, who survived to the age of 17 years or more, and were examined post mortem. In each case the cause of death is given at the right-hand side of the first line.

1. CHEVERS 1845 Adult woman Tuberculosis (subacute?)
   *Ductus*—about half as long as usual ligamentum, admitted a "common director."
   *Notes*—small mass of vegetations at pulmonary orifice of ductus which would act as valve preventing inflow to aorta from pulmonary artery.

2. BABINGTON 1847 34-yr.-old woman Subacute bact. endart.
   *Ductus*—extremely short (inoperable?).
   *Heart*—great dilatation and hypertrophy of both ventricles.
   *Complications*—slight aortic stenosis and coaretation.
   *Notes*—rheumatic history.

3. LUYS 1855 52-yr.-old woman Congestive failure
   *Ductus*—admitted little finger.
   *Heart*—right ventricle dilated and hypertrophic.
   *Notes*—many calcified plaques in pulmonary artery.

4. ALMAGRO 1862 23-yr.-old man Congestive failure
   *Ductus*—walnut-sized dilatation of pulmonary artery touched aorta and free communication existed between the lumens of the two vessels (inoperable).
   *Heart*—enormously enlarged, especially right ventricle, wall of which was 2.5 cm. thick.
   *Notes*—left lung atrophic.

5. DUROZIEZ 1862 40-yr.-old man Congestive failure
   *Ductus*—admitted a large pea.
   *Heart*—right auricle dilated, right ventricle greatly hypertrophied, *slight atrophy* of left ventricle.
   *Notes*—*no murmurs* heard in life.

6. SCHNITZLER 1864 43-yr.-old woman Congestive failure with erysipelas
   *Ductus*—diam. 5 mm. at pulmonary end, 6 mm. at aorta.
   *Heart*—hypertrophy right ventricle.
   *Notes*—many bony plaques in both aorta and pulmonary artery.

7. FAGGE 1873 45-yr.-old woman Congestive failure
   *Ductus*—short, widely patent.
   *Heart*—extreme dilatation right auricle, great enlargement tricuspid orifice, pulmonary orifice, and pulmonary artery. Both ventricles dilated and hypertrophic.

8. BUCHWALD 1878 21-yr.-old woman Subacute bact. endart.
   *Ductus*—easily admitted thick catheter.
   *Heart*—right side of heart almost normal, right ventricular wall thickness 3-4 mm., left side of heart much enlarged, ventricular wall 17 mm.
   *Complications*—aneurysm (size of hen's egg) of pulmonary artery.

9. FOULIS 1884 22-yr.-old woman Subacute bact. endart.
   *Ductus*—about 1/6 inch long, narrowest external diameter 1/4 inch, large end at aorta.

*Heart*—greatly enlarged, both ventricles hypertrophic, right auricle dilated. Extensive vegetations.

*Complications*—saccular aneurysm (size of large walnut) of pulmonary artery within pericardium.

*Notes*—murmurs disappeared almost entirely twenty-six days before death.

10. DARIÉR 1885 51-yr.-old woman Congestive failure

*Ductus*—round opening between aorta and pulmonary artery which were in apposition at the normal site of the ductus. (Inoperable.)

*Heart*—greatly enlarged, apex formed by both ventricles.

*Notes*—six or seven attacks of polyarticular rheumatism, but all valves normal. Fairly normal life until shortly before death.

11. W. H. WHITE 1885 53-yr.-old man Sudden death

*Ductus*—size of anterior tibial artery.

*Heart*—small, apparently entirely normal.

*Complications*—angina pectoris, with exacerbations and cyanosis.

*Notes*—died in attack of angina after one hour.

12. MURRAY 1888 36-yr.-old woman Subacute bact. endart.

*Ductus*—funnel-shaped, large end at aorta.

*Heart*—no right-sided cardiac hypertrophy.

*Notes*—calcification in wall of aortic side of ductus.

13. RICKARDS 1889 17-yr.-old man Subacute bact. endart.

*Heart*—435 gm.; left ventricle slightly hypertrophic.

*Complications*—mycotic aneurysm of branch of right pulmonary artery.

14. WILLIAMS 1890 40-yr.-old woman Pulmonary tuberculosis

*Notes*—multiple aneurysms of pulmonary artery and its branches.

15. SACHS 1892 21-yr.-old woman Subacute bact. endart.

*Ductus*—widely patent.

*Complications*—aneurysmal dilatation of main pulmonary artery, and oval aneurysm (2.5 cm. diam.) of right lower branch. Direct continuation of latter obliterated.

16. KIDD 1893 22-yr.-old woman Subacute bact. endart.

*Ductus*—opening to left pulmonary artery size of goose quill.

*Heart*—625 gm. Both sides hypertrophied and dilated, especially the left.

*Complications*—small saccular aneurysm of aorta close to ductus orifice. Saccular aneurysm, size of walnut, in lung, surrounded by healthy tissue. Few small tuberculous nodules, some softening to minute cavities, in lungs.

17. JOSEFSON 1897 66-yr.-old woman Sudden death

*Ductus*—4 mm. bore at pulmonary orifice, 6 by 10 mm. at aorta.

*Heart*—right ventricle hypertrophic; right auricle dilated.

*Notes*—this appears to be the oldest patient on record.

18. DRASCHE 1898 29-yr.-old woman Suicide

*Ductus*—fistula-like hole, 3 mm. bore. (Inoperable.)

*Heart*—small, flabby, thin-walled. No anomalies.

*Notes*—always well until vomited dark blood 6 months before suicide. Cause of this unexplained. Murmurs heard, but considered "accidental."

19. GIBSON 1900 31-yr.-old woman Pneumonia

*Ductus*—extremely short, admitted 12-14 bougie.

*Heart*—right ventricle dilated and hypertrophic.
*Complications*—delivered of seven-month-old child two weeks before death.

20. KRZYSZKOWSKI, J. 1902 17-yr.-old woman Subacute bact. endart. (?)
*Ductus*—diameter of a pencil.
*Heart*—hypertrophy of right ventricle, adhesive pericarditis at the base.
*Complications*—aneurysm of superior and anterior wall of pulmonary artery stem, multiple aneurysms of branches of pulmonary arteries. Marked degeneration in walls of these aneurysms.
*Notes*—all valves normal.

21. WEINBERGER 1903 37-yr.-old woman Congestive failure and pneumonia
*Ductus*—aneurysmal, thrombotic vegetations extending to wall of aorta and pulmonary artery to valve.
*Heart*—pulmonary valve insufficient.
*Complications*—repeated rheumatic and cardiac attacks for four weeks before pneumonia and failure.

22. HART 1904 23-yr.-old woman Subacute bact. endart.
*Ductus*—funnel-shaped, large end at aorta, patent to a middle-sized sound.
*Heart*—practically normal size, slight dilatation left ventricle. Embolic abscesses in myocardium.
*Notes*—author considered infection developed: aortic valves to ductus to pulmonary artery.

23. HART 1904 24-yr.-old woman Subacute bact. endart.
*Ductus*—funnel-shaped, large end at aorta, fresh embolus at pulmonary end extending into pulmonary artery.
*Heart*—both ventricles moderately dilated. Embolic abscesses in heart wall.
*Notes*—author considered infection developed: aortic valves to ductus to pulmonary artery.

24. LISSAUER 1905 24-yr.-old man Congestive failure
*Ductus*—15 mm. long, bore 6 mm. at pulmonary orifice, 4 mm. at aorta. At both orifices, folds of wall cut off about half of lumen.
*Heart*—moderate hypertrophy both ventricles, especially right.
*Complications*—bicuspid aortic valve. Aneurysm (size of hen's egg) of pulmonary artery. Slight hypoplasia of aorta. Marked emphysema both lungs.

25. GARIPUY 1907 28-yr.-old woman Congestive failure
*Ductus*—10 mm. diam., extremely short, pulmonary artery and aorta practically in apposition. (Inoperable?)
*Complications*—Sudden onset of failure few moments after delivery in second confinement. Died in twelve days.

26. DURNO and BROWN 1908 33-yr.-old man Ruptured pulmonary aneurysm
*Ductus*—widely patent, walls atheromatous.
*Heart*—very marked hypertrophy of right ventricle.
*Complications*—dissecting aneurysm of pulmonary artery ruptured into pericardium.
*Notes*—two weeks before death, attack of severe chest pain with vomiting: death in sleep, without warning.

27. WELLS 1908 42-yr.-old man Acute yellow atrophy
*Ductus*—16 mm. long, 5 mm. bore at pulmonary orifice, 8 mm. at aorta.

*Heart*—360 gm.; slight hypertrophy right ventricle.
*Notes*—cardiac symptoms unimportant in last illness.

28. HORDER 1909 42-yr.-old woman Subacute bact. endart.
*Heart*—510 gm.
*Notes*—clinical diagnosis, mitral disease.

29. MEAD 1910 26-yr.-old woman Congestive failure
*Ductus*—4 mm. bore at pulmonary orifice, 10 mm. at aorta.
*Heart*—395 gm.; both ventricles moderately hypertrophic, three ruptures of right ventricle, two ounces fluid blood in pericardial sac.
*Complications*—slight aortic and mitral stenosis, rheumatic history. Scoliosis. Complete paralysis left vocal cord.

30. SOMMERS 1910 45-yr.-old woman Subacute bact. endart.
*Ductus*—cone shaped, size of hazelnut at aortic orifice.
*Heart*—hypertrophy and dilatation of right ventricle.
*Notes*—ulcerative endocarditis of aortic valves and vegetations covering wall of ductus and of pulmonary artery all way back to pulmonary valves.

31. MOTZFELDT 1913 35-yr.-old man Sudden death; cause uncertain
*Ductus*—small caliber.
*Heart*—both ventricles slightly hypertrophic.
*Notes*—no mention of any murmur in previous medical history.

32. MOTZFELDT 1913 55-yr.-old woman Congestive failure
*Heart*—700 gm. Hypertrophy and dilatation of right ventricle.

33. MOTZFELDT 1913 32-yr.-old man Tuberculous pneumonia
*Ductus*—8 mm. diameter, extremely short, practically fistula between aorta and pulmonary artery. (Inoperable.)
*Heart*—590 gm. Both ventricles hypertrophic, especially right.
*Notes*—cardiac symptoms unimportant in last illness.

34. HAMILTON and ABBOTT 1914 19-yr.-old woman Subacute bact. endart.
*Ductus*—7.5 mm. long, "admitting a penholder."
*Heart*—slight hypertrophy and marked dilatation right ventricle. All endocardial structures normal.
*Complications*—mycotic aneurysm of pulmonary artery. Slight coarctation of aorta (6 cm. circumference at origin, 5 cm. at left subclavian, 4 cm. in descending portion).

35. STODDARD 1915 17-yr.-old woman Subacute bact. endart.
*Ductus*—8 mm. long; bore, 5 mm.
*Heart*—very slightly enlarged.

36. CAYLOR 1918 40-50-yr.-old woman Ruptured aortic aneurysm
*Ductus*—diameter 3.5 mm. at pulmonary artery; 6 mm. at aorta.
*Heart*—485 gm.; wall thickness, left ventricle, 11 to 24 mm., right ventricle, 4 to 8 mm.
*Complications*—ruptured aortic aneurysm, easily contained a whole fist.
*Notes*—diagnosis of patent ductus made twenty-one years before death, while still in apparently fair health; the thrill and machinery murmur disappeared, and were replaced only by poorly defined systolic murmur in pulmonary area.

37. BÄUMLER 1919 36-yr.-old woman Congestive failure
*Ductus*—wide, funnel-shaped, large end at aorta, no actual vessel (less than 0.5 mm. long).
*Heart*—much enlarged right ventricle; left normal.
*Complications*—miliary and nodal tuberculosis of lungs.
*Notes*—this patient observed eighteen years (when strong and well) until death.

38. HUBENY 1920 57-yr.-old woman Ruptured aortic aneurysm
*Heart*—marked left-sided cardiac hypertrophy and dilatation.
*Complications*—syphilitic aortic aneurysm observed, but not recognized in roentgenogram before rupture.
*Notes*—diagnosis of patent ductus made twenty years before death. Shadow of aortic aneurysm seen shortly before death, but ascribed to patent ductus.

39. WELLS 1922 50-yr.-old man Cerebrovascular accident
*Ductus*—coneshaped, 10 mm. at aortic end, 5 mm. near pulmonary orifice, latter closed to 1 or 2 mm. bore by fold of soft membrane protruding into pulmonary artery.
*Heart*—400 gm.; both ventricles dilated. No anomalies.
*Notes*—soft mitral murmur, not transmitted, only cardiac sign observed in few hours before death.

40. BOLDERO and BEDFORD 1924 29-yr.-old man Subacute bact. endart.
*Ductus*—15 mm. long.
*Heart*—greatly enlarged; both ventricles hypertrophic.
*Complications*—history of rheumatic fever.
*Notes*—2 small calcified areas in aortic wall near ductus. Blood pressure 200/90 before onset of subacute bact. endarteritis.

41. MOENCH 1924 29-yr.-old woman Ruptured pulmonary aneurysm
*Ductus*—admitted index finger.
*Heart*—mitral valve thickened; pulmonary valve bicuspid.
*Complications*—aneurysmal dilatation (3 inches in diameter) of pulmonary artery, ruptured into pericardium. Lungs congested.
*Notes*—small plaques of atheromata in aorta. No previous symptoms except slight exertional dyspnea.

42. TERPLAN 1924 35-yr.-old woman Subacute bact. endart.
*Ductus*—bore 2 mm.
*Heart*—hypertrophy and dilatation of left ventricle.

43. HAMMERSCHLAG 1925 51-yr.-old woman Subacute bact. endart.
*Ductus*—true mycotic aneurysm of ductus.
*Heart*—both ventricles hypertrophic.
*Notes*—histologic studies proved true aneurysm of ductus.

44. ROTH 1927 23-yr.-old woman Subacute bact. endart.
*Ductus*—5 mm. long, ulcerative endarteritis at pulmonary orifice.
*Heart*—moderately enlarged, fatty degenerative changes in myocardium.

45. von SCHULEZ 1928 25-yr.-old woman Congestive failure
*Ductus*—admitted pencil.
*Heart*—very marked hypertrophy and dilatation of right ventricle.
*Complications*—five months pregnant, surgical abortion planned after return to compensation, but she died before this was achieved.

46. P. D. WHITE 1928 65-yr.-old woman Cerebrovascular accident
*Ductus*—22.5 mm. long, 4 mm. bore at pulmonary artery, 10 mm. at aorta.
*Heart*—430 gm.; both ventricles hypertrophic. Severe sclerosis of coronaries, also aortic and mitral valves, aorta, and papillary muscles of left ventricle.
*Notes—pulmonary artery smooth and normal. First noted heart trouble at age of 40 years.*

47. KASAKOFF 1929 26-yr.-old woman Subacute bact. endart.
*Ductus*—5 mm. long; diameter, 5 mm.
*Heart*—both ventricles hypertrophic; wall thickness: left, 23 mm., right, 10 mm.

48. PALLASSE and CHANALEILLES 1930 47-yr.-old man Congestive failure
*Ductus*—practically fistula between aorta and pulmonary artery, 12 mm. diam. Organized clot almost obliterated free lumen. (Inoperable.)
*Heart*—700 Gm. Right ventricle more hypertrophic than left.
*Complications*—rheumatism at age 7.

49. WEISS 1931 33-yr.-old woman Subacute bact. endart.
*Heart*—350 Gm.
*Notes*—patient had five children, two miscarriages. Wassermann 4+. Disclike calcified plaque at aortic orifice of ductus.

50. FISCHER and SCHUR 1932 30-yr.-old woman Subacute bact. endart.
*Ductus*—easily patent to thick sound.
*Heart*—left ventricle hypertrophic.
*Notes*—questionable history of rheumatic fever few years earlier.

51. PERRY 1933 35-yr.-old woman Subacute bact. endart.
*Notes*—first diagnosed patent ductus and pulmonary tuberculosis.

52. d'AUNOY and von HAAM 1934 32-yr.-old man Subacute bact. endart.
*Ductus*—15 mm. long.
*Complications*—aneurysm of pulmonary artery. Syphilis.

53. BRODY and RANDELL 1935 66-yr.-old woman Congestive failure
*Ductus*—14 mm. long, diameter 4 mm. at pulmonary artery, 9 mm. at aorta.
*Heart*—both ventricles enlarged.
*Notes*—congenital polycystic kidney, ureter absent. No symptoms except palpitation until age of 62 years. Died at age of 65 years, 11½ months.

54. HINES and WOOD 1935 18-yr.-old woman Subacute bact. endart.
*Ductus*—bore about 2-3 mm.
*Heart*—great dilatation of both sides; not much hypertrophy.
*Notes*—pulmonary valve leaflets completely destroyed, pulmonary artery and ductus almost filled with vegetations, other valves normal, two small polypoid vegetations on aortic side of ductus.

55. MALLORY 1938 21-yr.-old woman Subacute bact. endart.
*Ductus*—aorta and pulmonary artery in apposition and communicating by a small round hole at the usual site of the ductus arteriosus. (Inoperable.)

56. GRENET, LEVENT and JOLY 1939 17-yr.-old woman Subacute bact. endart.
*Ductus*—5 to 10 mm. long; small caliber.
*Heart*—both sides dilated and hypertrophic.
*Notes*—no dilatation of pulmonary artery.

57. BETTINGER 1941 40-yr.-old woman Congestive failure
*Ductus*—8 mm. long; 7.5 mm. in diameter. Wall rigid with calcifications.
*Heart*—extreme hypertrophy right ventricle (wall thickness up to 20 mm.).
*Complications*—died of failure seven days after pelvic operation from which she failed to rally.

## Appendix B

### Atypical patency of the ductus in adults

1. CHEVERS 1845 Young man Pneumonia
*Ductus*—about 4 mm. communication between aorta and pulmonary artery, which were in apposition at usual site of ductus. (Inoperable.)
*Complications*—considerable constriction of aorta above site of communication with pulmonary artery.

2. HEBB 1893 40-yr.-old man Pulmonary tuberculosis
*Ductus*—aneurysmal (size of walnut) filled with firm laminated clot.
*Heart*—verrucose endocarditis of aortic valve.
*Complications*—complete obliteration of left branch of pulmonary artery and marked stenosis of left branch at its origin.
*Notes*—no cardiac anomaly suspected during life.

3. HOCHHAUS 1893 24-yr.-old man Subacute bact. endart.
*Ductus*—diameter about 6 mm. in middle, 7 mm. at pulmonary end, 14 mm. at aortic end.
*Heart*—greatly dilated and hypertrophic.
*Complications*—marked stenosis of aortic arch just before orifice of the ductus.
*Notes*—there was a prominent diastolic murmur as well as the usual prolonged systolic murmur.

4. WAGENER 1903 38-yr.-old woman Pneumonia
*Ductus*—16 mm. long, 7 mm. bore except at pulmonary orifice, which was closed by membrane except for pinhole communication.
*Heart*—normal.
*Notes*—no dilatation of pulmonary artery.

5. WAGENER 1903 42-yr.-old man Postoperative peritonitis
*Ductus*—funnel-shaped pouch in aorta projected into pulmonary artery; this pouch was pierced by two very small holes. Considered patent ductus by pathologist.
*Heart*—chronic endocarditis of aortic valves, slight stenosis of aortic and pulmonary valves.
*Notes*—no murmurs in life.

6. MOENCKEBERG 1924 35-yr.-old man Congestive failure?
*Ductus*—aneurysmal (half size of apple), filled with clot, not patent throughout. No trace of ligamentum arteriosum.
*Heart*—marked eccentric (right-sided) hypertrophy.
*Notes*—marked paralysis of left vocal cord. Clinical diagnosis was "war nephritis."

7. HALL 1926 32-yr.-old man Congestive failure

*Ductus*—bore, 3 mm.

*Heart*—greatly enlarged (860 gm.), chiefly left ventricle. Aortic ring dilated and insufficient.

*Complications*—healed dissecting aneurysm of aorta near valve.

8. PAUL 1930 36-yr.-old man Erysipelas

*Ductus*—patent to a thick sound.

*Heart*—770 gm., both sides equally enlarged.

*Complications*—isthmus stenosis of aorta sharply confined to point opposite orifice of ductus.

*Notes*—rheumatic fever at 28 years.

9. ULRICH 1932 23-yr.-old man Sudden failure

*Ductus*—formed principal source of blood supply to the descending aorta.

*Heart*—870 Gm., both sides greatly enlarged, but right more so than left; right ventricle wall thickness 10 to 20 mm., left 15 to 30 mm.

*Complications*—aortic arch greatly constricted between left subclavian and insertion of ductus, hypoplastic descending aorta. Cirrhosis of the liver (2,725 gm.). Bundle branch block.

*Notes*—worked as farm laborer without trouble until development of ascites.

10. GRAHAM 1940 31-yr.-old man Hem. at operation

*Ductus*—aneurysmal, filled with partly organized clot, pulmonary end obliterated.

*Heart*—moderate hypertrophy left ventricle, patent foramen ovale (probably functionally closed), right aortic arch.

*Notes*—preoperative diagnosis was mediastinal tumor.

*(See discussion on page 205.)*

# THE RESULTS OF SURGICAL TREATMENT OF PATENCY OF THE DUCTUS ARTERIOSUS COMPLICATED BY SUBACUTE BACTERIAL ENDARTERITIS

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## INTRODUCTION

THE first surgical cure of subacute bacterial endarteritis involving a patent ductus arteriosus was reported by Touroff and Vesell[1] in 1940. Although additional operative cures have been recorded since then by the author and others,[2-8] statistics concerning the general results of surgical treatment of infected patent ductus arteriosus are not as yet available. Accordingly, it may be of interest to report a series of eleven patients who have been operated upon during the past two and one-half years.

When the first of these patients was subjected to operation (in January, 1940), the only reference in the literature to the surgical treatment of patency of the ductus arteriosus complicated by subacute bacterial endarteritis was a report of a single unsuccessful attempt at ligation of the duct by Graybiel, Strieder, and Boyer[9] (1938).† Thus, in the absence of any knowledge of how the superimposed infection might respond to surgical therapy, operation was undertaken purely empirically. Much to our gratification, the patient not only survived, but also recovered promptly. Subsequently, ten additional patients were operated upon; and it is the purpose of the present communication to set forth the results which were obtained and to discuss some of the factors which appear to influence the outcome of operation. At the outset, it may be stated that although not all of our patients were cured, the value of surgical therapy in properly selected cases was firmly established.

## FACTORS INFLUENCING THE OUTCOME OF OPERATION

In a previous communication,[6] it was indicated that proper evaluation of surgical therapy necessitates an appreciation of the fact that the pathologic process in the ductus and adjoining structures may vary considerably in severity and extent, and that the outcome of operation is influenced largely by such pathologic changes. Abbott[11] has pointed out that vegetations usually develop initially at the pulmonic end of the ductus and in the adjacent portions of the pulmonary artery, and that, at a later stage of infection, they may involve the cardiac valves or ex-

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†The first successful ligation of a patent ductus arteriosus (uncomplicated by infection) was reported by Gross and Hubbard[10] in 1939.

tend into the aorta. It has already been demonstrated that, if operation is performed while the vegetations remain confined to the pulmonic end of the ductus and the pulmonary artery, a cure may be anticipated fairly regularly.[6] On the other hand, if vegetations have already spread to the cardiac valves or into the aorta, operation fails to prevent the growth of these new vegetative lesions,[12] and the latter continue to act as foci from which infective material is released into the peripheral circulation.

The severity and extent of pathologic changes involving the ductus and adjacent tissues, in addition to influencing the late results of surgical treatment, also determine in large measure the actual hazards of the operation. In previous communications,[6, 12] it was pointed out that the greatest of these dangers is accidental hemorrhage resulting from injury of the ductus as the latter is being separated from the adjacent tissues—chiefly the pulmonary artery and left main bronchus—preliminary to ligation. In the earliest stages of infection, the inflammatory process involves only the intima of the ductus. Subsequently, however, it may involve more and more of the thickness of the wall of the ductus. At a still later stage, the inflammation may extend to the adventitia and surrounding tissues; the ductus then usually becomes adherent, in varying degree, to the adjacent structures. As the wall of the ductus becomes extensively diseased, it tends to become indurated and friable; and the local inflammatory process sometimes may be so destructive that mycotic aneurysms[11] are formed. Friability of the ductus (or aneurysm) and adherence to the surrounding structures greatly increase the likelihood of inadvertent tearing of the ductus as the latter is being manipulated. The hemorrhage which results from such an accident is often difficult to control and is not infrequently fatal. From all of the foregoing it is apparent that the earlier the operation is performed, the greater is the likelihood of cure and the less are the chances of operative hemorrhage. In this connection it is germane to discuss briefly the danger of prolonged chemotherapy.

It is now rather generally agreed that if chemotherapy is to prove curative in cases of subacute bacterial endarteritis, evidence of infection will subside and blood cultures will become sterile fairly promptly. Accordingly, if this does not occur within two or three weeks, the likelihood of recovery becomes increasingly remote. In spite of this oft-repeated dictum, there is a general tendency to continue the administration of sulfonamide drugs after the latter have proved ineffectual. Such a policy may be excusable in cases of subacute bacterial endarteritis of the usual type, because other forms of treatment are of little or no value. In cases of subacute bacterial endarteritis involving a patent ductus, however, prolonged chemotherapy may jeopardize the patient's chances of recovery by delaying operation unduly. Judging from the general lack

of effectiveness of preoperative chemotherapy in the cases of the present series, and in other cases in which no operation was done, I am of the opinion that the interests of the patient are best served by proceeding with operation as soon as the diagnosis of superimposed infection has been established. Although this viewpoint may appear radical, it is based upon the following observations: (1) the low incidence of recovery with chemotherapy alone, (2) the variable outcome in cases in which chemotherapy is employed for long periods prior to operation, and (3) the high incidence of recovery after operation, when the latter is performed *before* vegetations have spread to the cardiac valves or into the aorta. The effectiveness of surgical therapy in the last group is demonstrated particularly by the fact that recovery ensues without chemotherapy after operation (Table II). To summarize, it may be stated that the role of chemotherapy should be that of an adjuvant, and not a substitute for operation.

### PREOPERATIVE DATA

Of the eleven patients in this series, eight were women. The patients ranged in age from 9 to 63 years.* Five were in the third decade, two in the fourth decade, and one each in the first, second, sixth, and seventh decades of life. It appeared significant that, in nine of the eleven patients, infection occurred during or after the third decade.†

In ten cases the duration of infection, from the time of onset of clinical manifestations to the time of operation, varied between thirty-one (+) days and five months. In the remaining case (Case 11), which was altogether unique, infection had been present for two years prior to operation.‡ Despite the fact that the majority of the blood cultures had been positive since the onset of the illness, the patient remained in surprisingly good physical condition and exhibited few of the stigmata of subacute bacterial endarteritis (endocarditis) of long duration.

Five patients had spontaneous pulmonary embolism prior to operation (Cases 3, 6, 7, 10, and 11). One of these also developed splenic infarction (Case 10). Another patient had renal infarction (Case 2). The preoperative peripheral embolism in the last two cases (Cases 2 and 10) was

*The wide variation in age (9 to 63 years) re-emphasizes a point made in previous communications,[6, 12] namely, that subacute bacterial endarteritis may occur at any age, and that it constitutes a perpetual threat to the patient with a patent ductus arteriosus. In this connection, it is to be stressed that the patient with a patent ductus arteriosus should be kept under observation throughout life, and a blood culture taken promptly if fever of obscure origin appears.

†This is assumed to be caused by two factors. The first is that foci of *Streptococcus viridans* infection (teeth, tonsils, etc.), which presumably constitute the original portal of entry, are much more common in adults than in children. The second is that atheromatous plaques, which constitute the primary sites of development of vegetations, usually do not make their initial appearance until adult life.

‡Two patients with the chronic form of subacute *Streptococcus viridans* infection were also operated upon. Both presented typical stigmata, including profound anemia, café-au-lait color, repeated crops of petechiae, great splenic enlargement, amyloidosis, renal involvement, and clubbing of the fingers. In one case, the diagnosis of infection of a patent ductus arteriosus was confirmed at operation. In the other, the ductus was not open, and it was assumed that the congenital cardiac lesion was, in all probability, a septal defect. These two patients were placed in a special experimental group in advance of operation because there seemed little likelihood that they would recover completely even if operation were carried out successfully. They will not be discussed here, but will be the subject of a separate report.

attributed to vegetative lesions upon the mitral and aortic valves; and the persistence of the latter lesions after operation accounted for the failure of these patients to recover from their infection.

Evidence of cardiac failure was present in three cases (Cases 3, 6, and 7) at the time of operation; and it appears significant that this occurred in the two oldest patients of the series (aged 51 and 63 years, respectively). Both of the latter were free of manifestations of circulatory failure during childhood and early adult life. Thus, although compensation was adequate in the beginning, cardiac failure supervened as the myocardium began to undergo late degenerative changes. Incidentally, the fact that infection and cardiac failure first occurred so late in life constitutes a powerful argument in favor of prophylactic operation during childhood.

Ten patients received chemotherapy prior to operation (either before or after admission to the hospital) without significant effect; the remaining patient (Case 1) did not receive chemotherapy. At the time of operation, all patients presented clinical and laboratory evidence of active infection and all had positive blood cultures *(Streptococcus viridans)*.

In all cases, the characteristic "machinery" murmur of patent ductus arteriosus was present. Several of the patients had additional soft systolic murmurs (at the apex or base) which were considered to be of little significance. In two cases (Cases 2 and 10), the presence of characteristic murmurs led to the additional preoperative diagnosis of secondary, vegetative valvular involvement.* It was assumed in advance that operation would fail in these two cases; but, in order to either establish or disprove this point, it was decided to proceed.

TABLE I

RESULTS OF SURGICAL TREATMENT IN ELEVEN CASES

| | |
|---|---|
| A. Operative Survivals | 9 |
| Cured | 6 |
| (See Table II.) | |
| Not Cured | 3 |
| (a) Two patients with preoperative spread of vegetations to the cardiac valves | |
| (b) One patient with preoperative extension of vegetations into the aorta | |
| (See Table III.) | |
| B. Operative Deaths | 2 |
| Both caused by hemorrhage from injury to a friable, adherent ductus (prior to modification of operative technique). | |
| (See Table III.) | |

*The diagnosis in these two cases was further substantiated by the occurrence of peripheral embolism prior to operation.

## THE RESULTS OF OPERATION

The operation consisted of ligation of the ductus in nine cases and division of the ductus in two (Cases 1 and 7). Among the eleven cases, there were nine operative survivals and two operative deaths (from hemorrhage).

The two fatalities occurred early in the series[12] (Cases 3 and 4), before the present modification of operative technique was developed.[13] Postmortem examination in Case 3 disclosed that the vegetations were confined exclusively to the ductus and pulmonary artery. At autopsy in Case 4, vegetations were found at the above sites; and a few pin-point verrucae, the significance of which was uncertain, were noted upon the pulmonic valve (Table I).

Of the nine surviving patients, six recovered from their infection.* In none of the latter cases was recovery attributable to chemotherapy.† Furthermore, the rapidity with which the blood cultures became sterile was startling (see Table II). (This aspect of the first five cases has already been presented briefly.[1, 6, 7, 8] A detailed report of the bacteriologic investigations in all eleven cases will be published in the near future.)

Recovery in four of the six cases was entirely uneventful. In the remaining two cases, minor complications occurred. These consisted of two attacks of mild, left-sided pulmonary infarction in Case 1, and of a superficial wound infection in Case 5. The longest postoperative stay in the hospital was thirty-four days (Case 5); the shortest was thirteen days (Cases 6 and 8).

All six patients have had repeatedly negative blood cultures, have been free of clinical and laboratory evidences of infection, and are carrying on normal activities at the present time. The two patients who had circulatory failure prior to operation (Cases 6 and 7) are entirely free of this complication. The follow-up period varies from three to twenty-nine months (see Table II).‡

Three of the nine surviving patients (Cases 2, 9, and 10) continued to have positive blood cultures after operation. Prior to operation, two of them (Cases 2 and 10) had peripheral embolism, and presented apical and basal murmurs indicative of valvular involvement, in addition to

*The rationale of ligation of the ductus when a patent ductus arteriosus is complicated by subacute bacterial endarteritis has been discussed elsewhere.[14]

†One of these patients (Case 1) received 9 grams of sulfapyridine on the fifth postoperative day, after all postoperative blood cultures prior to that time had remained sterile.[1] Another patient (Case 5) received 10 grams of sulfapyridine on the twelfth postoperative day, after all postoperative blood cultures prior to that time also had been negative.[8] (In Case 1, the drug was employed because of an acute postoperative febrile reaction. In Case 5, it was used because of continuing fever of obscure origin.) In view of the already sterile postoperative blood cultures, before chemotherapy was begun, it appears warranted to maintain that the sulfonamides played no role in the recovery of either of these patients. In the remaining four cases, chemotherapy was not employed after operation. To the best of my knowledge, these are the only cases so far reported in which chemotherapy was withheld after operation in an attempt to test the effectiveness of operative therapy alone. The results demonstrate conclusively that operative occlusion of the ductus, per se, is curative.

‡Cardiovascular studies in these cases will be reported in detail in a separate communication.

TABLE II

SUBACUTE STREPTOCOCCUS VIRIDANS ENDARTERITIS SUPERIMPOSED ON PATENT DUCTUS ARTERIOSUS

6 CURED PATIENTS

| CASE, NAME AGE, SEX | DURATION OF INFECTION | PRE-OPERATIVE CHEMOTHERAPY | BLOOD CULTURES | | OPERATION DATE AND TYPE | POST-OPERATIVE BLOOD CULTURES | | POST-OPERATIVE CHEMOTHERAPY | RESULT |
|---|---|---|---|---|---|---|---|---|---|
| | | | NO. OF COLONIES | LAST PRE-OPERATIVE CULTURE | | INITIAL CULTURE(S) | SUBSEQUENT CULTURES | | |
| 1<br>S. S., 29<br>Female | 3 Months | None | 50-400 | 1/24/40<br>Heavily positive | 1/27/40<br>Division of ductus | 1/29/40<br>Sterile | 6<br>All sterile | Sulfapyridine 9 gm. on 5th day (blood cultures already sterile) | Well<br>28½ Months |
| 5<br>F. S., 29<br>Female | 31+ Days | Poorly tolerated (Sulfapyridine) | 0-177 | 6/14/41<br>9:00 A.M.<br>80 col./c.c. | 6/14/41<br>3:15 P.M.<br>Ligation of ductus | 6/14/41<br>6:15 P.M.<br>Sterile | 11<br>All sterile | Sulfapyridine 10 gm. on 12th day (blood cultures already sterile) | Well<br>12 Months |
| 6<br>G. O., 51<br>Female | 8 Weeks | Poorly tolerated (Sulfapyridine sulfathiazole) | 40-52 | 8/25/41<br>52 col./c.c. | 9/4/41<br>3:30 P.M.<br>Ligation of ductus | 9/4/41<br>4:10 P.M.<br>Sterile | 4<br>All sterile | None | Well<br>9 Months |
| 7<br>J. Z., 18<br>Female | 4 Months | Well tolerated (Sulfathiazole) | 70-120 | 9/27/41<br>2:00 P.M.<br>120 col./c.c. | 9/27/41<br>3:49 P.M.<br>Division of ductus | 9/27/41<br>4:00 P.M.<br>1 col./c.c.<br>4:30 P.M.<br>1 col./c.c. | 7<br>All sterile | None | Well<br>8½ Months |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 8<br>H. N., 9<br>Male | 5 Weeks | Well tolerated<br>(Sulfadiazene) | 2·88 | 1/9/42<br>3:02 P.M.<br>Heavy growth in flask | 1/9/42<br>3:04 P.M.<br>Ligation of ductus | 1/9/42<br>3:14 P.M.<br>Sterile<br>3:34 P.M.<br>Sterile<br>4:10 P.M.<br>Sterile<br>5:10 P.M.<br>1 col./4 c.c.<br>10:10 P.M.<br>1 col./4 c.c. | 1/10, 11, 13, 15<br>Sterile<br>---<br>1/17<br>1 col./20 c.c.<br>---<br>Thereafter 7<br>All sterile | None | Well<br>5 Months |
| 11<br>H. S., 31<br>Male | 24 Months | Well tolerated<br>(Sulfadiazene, sulfathiazole, sulfapyridine & sulfanilamide) | 0·143 | 3/24/42<br>2:58 P.M.<br>54 col./c.c. | 3/24/42<br>3:10 P.M.<br>Ligation of ductus | 3/24/42<br>3:16 P.M.<br>7 col./c.c.<br>---<br>3:26 P.M.<br>Plates sterile<br>Flasks positive<br>---<br>3:43, 4:10, 5:10, 6:10, 8:10 & 11:10 P.M.<br>All sterile | 3/25, 26, 28, 29, 31 & 4/3<br>Sterile<br>---<br>4/7<br>Flask positive<br>---<br>Thereafter 4<br>All sterile | None | Well<br>11 Weeks |

TABLE III

SUBACUTE STREPTOCOCCUS VIRIDANS ENDARTERITIS SUPERIMPOSED ON PATENT DUCTUS ARTERIOSUS
5 OPERATIVE FAILURES

| CASE NAME SEX AGE | DURATION OF INFECTION | PREOPERATIVE CHEMOTHERAPY | PREOPERATIVE BLOOD CULTURES | OPERATION DATE AND TYPE | POSTOPERATIVE BLOOD CULTURES | CAUSE OF FAILURE | RESULT FOLLOW-UP |
|---|---|---|---|---|---|---|---|
| 2<br>G. F.<br>Female<br>29 | 5 Weeks | Well tolerated (sulfapyridine) | 15-50 col./c.c. | 2/8/40<br>Ligation of ductus | All positive, despite chemotherapy | Vegetations upon aortic valve | Died of original infection 8 mo. after operation |
| 3<br>A. S.<br>Female<br>63 | 5 Months | Well tolerated (sulfanilamide, sulfapyridine and heparin) | 6-30 col./c.c. | 3/16/40<br>Attempted ligation of ductus | → | Operative hemorrhage (from a friable, adherent ductus) | Death. Vegetations confined to ductus and pulmonary artery |
| 4<br>J. S.<br>Female<br>24 | 3 Months | Well tolerated (sulfanilamide and sulfapyridine | 32-72 col./c.c. | 4/8/40<br>Attempted ligation of ductus | → | Operative hemorrhage (from a friable, adherent ductus) | Death. Vegetations in ductus and pulmonary artery and upon pulmonic valve (pinpoint verrucae) |
| 9<br>C. B.<br>Female<br>20 | 9 Weeks | Well tolerated (sulfadiazine) | 25-30 col./c.c. | 2/19/42<br>Ligation of ductus | All positive, despite chemotherapy | Vegetations within aorta (or aortic end of ductus) | Unimproved 16 weeks after operation |
| 10<br>I. A.<br>Male<br>33 | 4½ Months | Well tolerated (sulfapyridine and sulfathiazole) | 15-27 col./c.c. | 3/3/42<br>Ligation of ductus | All positive, despite chemotherapy | Vegetations upon mitral and aortic valves | Unimproved 14 weeks after operation |

evidences of a patent ductus. The last patient (Case 9) presented no such preoperative phenomena, and it was, therefore, concluded that the continuing postoperative bacteremia was not caused by valvular vegetations, but by vegetations within the ductus on the aortic side of the ligature. This conclusion appeared to be substantiated by the occurrence, for the first time, of splenic infarction nine days after operation.*

The subsequent fate of these three patients is indicated in Table III.

## DISCUSSION

Prior to operation, seven of the nine surviving patients presented no evidence of vegetative valvular lesions or peripheral embolism. (Red-centered petechiae are not classed as embolic lesions.) Of these seven patients, six were cured, and one continued to have active bacteremia, due to vegetations at the aortic end of the ductus. The remaining two of the nine patients presented auscultatory evidence of valvular lesions and had peripheral embolism prior to operation. These patients continued to have bacteremia after operation.

The foregoing analysis re-emphasizes the fact that when vegetations remain confined to the pulmonic end of the ductus and pulmonary artery, peripheral embolism is not likely to occur, and operation, if carried out successfully, is likely to be followed by recovery from the infection. On the other hand, when vegetations have spread to the cardiac valves, mitral or aortic, peripheral embolism occurs and characteristic murmurs are likely to be present prior to operation. In cases of the latter type, operation does not benefit the patient.

When vegetations are present at the aortic end of the ductus, they may produce no unusual murmurs and may not result in peripheral embolism prior to operation. In such cases, therefore, it may be impossible to make the diagnosis. In this connection, it should be pointed out that when vegetations actually extend into the aorta they may not produce new murmurs, but they are often responsible for peripheral embolism prior to, and after, operation. In such cases, also, operation is not advisable.

It appears that spread of vegetations to the pulmonic valve is difficult to recognize prior to operation. Thus, in Case 4, in which several verrucae were present at that site, the patient presented no unusual manifestations. Although valvular murmurs may have been present, they might easily have been obscured by the loud, roaring machinery murmur. Likewise, if emboli were being thrown off, they were probably trapped in the lung, so that peripheral embolic manifestations were pre-

*In view of the fact that the current through the ductus flows from the aorta toward the pulmonary artery, it is assumed that emboli derived from vegetations close to the aortic end of the ductus normally are swept into the pulmonary circuit.[15] After the ductus is ligated, however, vegetations which remain on the proximal side of the ligature release their emboli into the aortic blood stream. This appears to explain the initial occurrence of peripheral embolism after operation in Case 9. If peripheral embolism had been the result of vegetations within the aorta, one would expect it to have occurred prior to operation as well as afterward.

vented. Whether or not a patient with right-sided, vegetative valvular lesions can be cured by operation still remains uncertain.

Although the secondary development of vegetations upon the cardiac valves is most likely to occur when the infection is prolonged, it appears that the duration of infection is not the only factor. For example, in Case 2, vegetations developed upon the aortic valve after only five weeks of illness; whereas, in Case 11, spread did not occur despite the fact that the infection had been present for two years. It is apparently significant that the clinical course in Case 2 was of the severely septic type, whereas in Case 11 it was unusually mild. Thus, severity of infection appears to be an additional factor in determining the rapidity of spread to the valves. This point was substantiated by a review of the remaining cases of the series. Finally, the configuration of the ductus seems to play a role in determining the outcome of the operation.

Abbott[11] has demonstrated that the ductus may vary in shape from a well-defined tubular structure to an arteriovenous fistula in which the ductus consists merely of an opening between the aorta and pulmonary artery. This has been demonstrated at operation, also. Whereas vegetations develop initially at the pulmonic end of a ductus of average length, those within a short ductus are likely to involve practically its entire length. Thus, when a short ductus is ligated, it may be impossible to place the ligature beyond the vegetations at the aortic end, and so exclude the vegetations from contact with the aortic blood current. As a result, any vegetations which remain on the proximal side of the ligature continue to launch infective material directly into the aorta, and the bacteremia persists. This was apparently the cause of failure in Case 9, in which the ductus was found at operation to be relatively short in proportion to its diameter and joined to the aorta by a wide funnel-like mouth.

### INDICATIONS AND CONTRAINDICATIONS TO OPERATION

It has already been demonstrated that the mere presence of additional cardiac murmurs is not a reliable indication of the existence or location of new vegetative lesions. Thus, chief reliance must be placed upon the occurrence of peripheral embolism in deciding whether or not operation should be performed. If peripheral embolic lesions are unquestionably present, operation appears to be contraindicated. On the other hand, if such embolic lesions have not occurred, the patient is entitled to operation even if murmurs, suggesting the presence of valvular lesions, exist. Although operation in doubtful cases may not always result in recovery from infection, it offers the patient his only remaining chance and, therefore, should be undertaken without hesitation.

Aside from incontrovertible evidence of spread of vegetations, as indicated by the occurrence of peripheral embolic lesions, the only absolute contraindication to operation is clear-cut evidence of the presence of

associated, major congenital cardiovascular anomalies, for which the patent ductus acts as a compensating lesion. Under the latter circumstances, the current through the ductus flows from the pulmonary artery into the aorta, and the resultant inadequate oxygenation of the blood produces cyanosis and clubbing of the fingers. Ligation of the ductus in such cases usually leads rapidly to circulatory embarrassment and death.

In certain cases, patency of the ductus arteriosus may be associated with some minor congenital cardiovascular anomaly. If the presence of an associated cardiovascular anomaly is suspected or has been demonstrated by angiocardiography, but the patient is not cyanotic, it may be concluded that the lesion in question is of minor significance and that it is safe to proceed with operation. In this connection, however, it must be remembered that vegetations are prone to develop at sites of associated cardiac anomalies, regardless of whether the latter are major or minor. If vegetations already are present at such sites, the course of events is likely to be as little influenced by ligation of the duct as it is in cases in which vegetations have spread to the cardiac valves or aorta. If vegetations have not already become engrafted upon the associated minor anomaly, however, operation may prove curative.

There still seems to be some hesitation, on the part of certain internists, to advise surgical treatment of patency of the ductus arteriosus when the ductus is the seat of subacute bacterial endarteritis. This may be due primarily to fear that the surgical procedure is of such magnitude that it may not be withstood by patients who are either very acutely ill or are debilitated by prolonged infection. The cases described herein demonstrate that such an attitude is no longer justifiable; for, with the exception of two patients who died of hemorrhage early in the series, the remainder withstood the operation without difficulty. In Case 6, for example, the patient, aged 51 years, suffered not only from infection, but also from cardiac failure and recent pulmonary infarction.[7] Case 7 demonstrates, in a convincing manner, that poor general physical condition is not a contraindication to operation. On the contrary, rapid worsening of the patient's condition and the prospect of early fatality constitute powerful arguments in favor of prompt surgical intervention. Because of certain unusual features, Case 7 appears worthy of brief presentation.

## REPORT OF CASE

*History.*—J. Z., a native-born white girl, aged 19 years, was admitted to the medical service of Beth Israel Hospital September 24, 1941. She was known to have had heart trouble since the age of one and one-half years. Since earliest childhood, she had been thin and underdeveloped, and she suffered from dyspnea and fatigue on mild exertion. The remainder of the past history was irrelevant.

About four months prior to admission she developed irregular fever and lassitude and began to lose weight. At that time, the diagnosis of patency of the ductus arteriosus was made, but no specific treatment was recommended (Fig. 1). After two months of continuing symptoms, she had an attack of severe pain in the left side of the chest. Two weeks later she was admitted to another hospital, suffering from

sweats, irregular fever (ranging from 101° to 105° F.), chills, pain in the left side of the chest, and dyspnea. At that time, four blood cultures were positive for *Streptococcus viridans*, and roentgenologic examination of the chest revealed evidence of patency of the ductus arteriosus and left-sided pulmonary infarction. The electrocardiogram at first was negative, but one month later revealed right axis deviation.

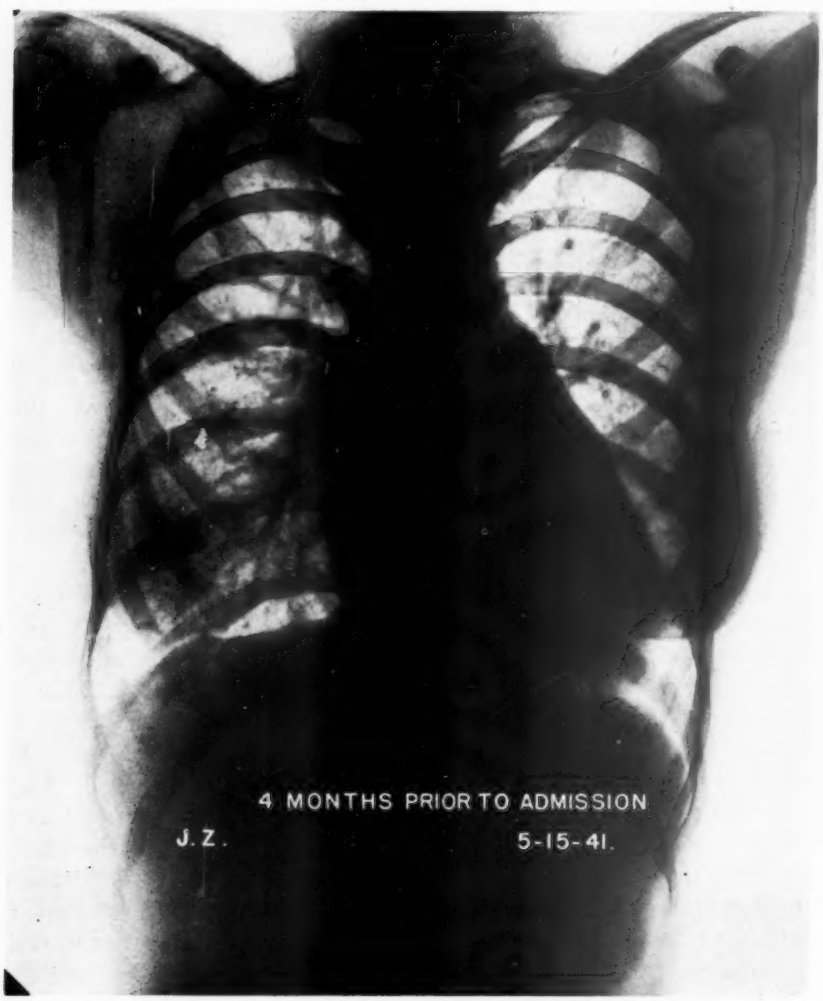


Fig. 1.—Roentgenogram of chest four months prior to admission to the hospital. Note enlargement of the heart, prominence of the region of the pulmonic conus, and pulmonary vascular congestion.

The blood pressure on admission was 130/70, but later the diastolic pressure could not be obtained. Large doses of sulfathiazole were administered throughout the hospital stay, but no significant effect was produced. At the end of five weeks she was discharged with the diagnosis of "Patent Ductus Arteriosus. Subacute Bacterial Endocarditis."*

*The author is indebted to Dr. Louis Greenstein, of Brooklyn, N. Y., for information concerning the details of the patient's illness prior to operation.

*Examination.*—On admission to Beth Israel Hospital, the patient appeared not only very acutely, but also chronically, ill. The temperature was 103.2° F., the pulse rate, 114, and the respiratory rate, 24. She was septic, dyspneic, cachectic, pale, and perspired profusely (Fig. 2).

The heart was slightly enlarged. The apex beat was felt immediately outside the midclavicular line in the fifth intercostal space, and was forceful and heaving. In the second intercostal space, 2 or 3 cm. to the left of the sternal border, a systolic thrill was present. A continuous machinery murmur, which was louder in systole than in diastole, was heard in the same area. The pulmonic second sound was greatly accentuated. The machinery murmur was transmitted upward as far as the first rib, and downward to the fourth rib medially. It was audible as far as the left sternal border, and laterally to the midclavicular line.

Fig. 2.—Patient on admission to hospital.

The blood pressure was 122/46-0. After resistive exercise of the leg (modified Bohn test), the blood pressure was 144/38-0. Examination of the lungs revealed medium-sized râles at the left base. The area of splenic dullness was increased. No petechiae were noted, and the remainder of the physical examination failed to disclose anything significant.

*Laboratory Data.*—A teleoroentgenogram revealed marked enlargement of the left ventricle and pulmonary conus. A moderate sized area of infiltration, caused by pulmonary infarction, was noted adjacent to the left cardiac border. Moderate pulmonary vascular congestion was present (Fig. 3). Kymographic examination revealed marked pulsation of the pulmonary artery. The four lead electrocardiogram revealed slight right axis deviation, a small, inverted $T_1$, and a large, inverted $T_4$. The phonocardiogram disclosed a continuous murmur, systolic and diastolic, of maximum intensity over the second intercostal space, 2 cm. beyond the left sternal border. The circulation time was normal. The urine was normal. The blood contained 3,590,000 erythrocytes per cubic millimeter, and the hemoglobin content was 55 per

cent. The leucocyte count was unaltered. The erythrocyte sedimentation rate was 28 mm. in 45 minutes. The Wassermann, Kline, and Kahn tests gave negative results. A blood culture, taken on the day of admission, revealed 70 colonies of *Streptococcus viridans* per cubic centimeter after 48 hours' incubation. Because of the above observations, the admission diagnosis of patency of the ductus arteriosus, with superimposed, subacute, *Streptococcus viridans* endarteritis, was confirmed.

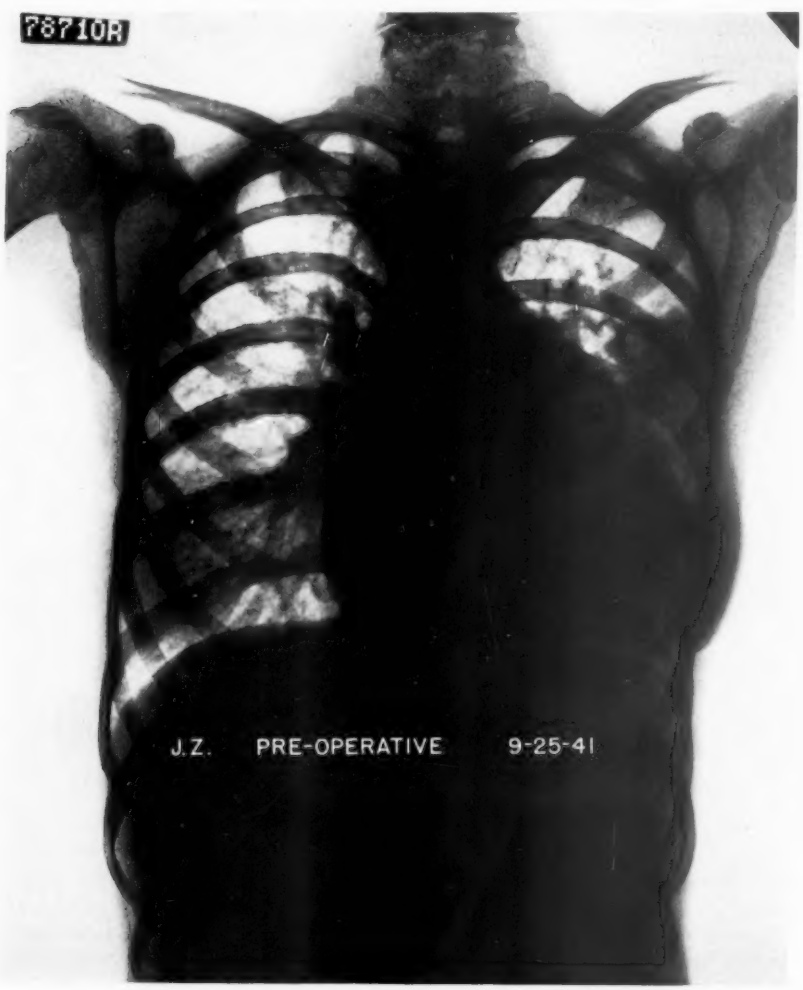


Fig. 3.—Roentgenogram taken on admission. Note the great increase in the size of the heart and the presence of a pulmonary infarct immediately adjacent to the left cardiac border.

It was decided to subject the patient to operation without delay, for the following reasons: (1) the septic, progressively unfavorable course, (2) the failure to respond to prolonged and intensive chemotherapy prior to admission to the hospital, (3) the increasing circulatory involvement, as indicated by the progressive cardiac enlargement, the development of right axis deviation, and the increasing pulse pressure, (4) the persistently positive blood cultures, (5) the development of pulmonary infarction, and (6) the absence of evidence of other associated congenital cardiac

defects or active valvular lesions. Although the risk of operation appeared great, it also seemed that continuation of conservative therapy would almost inevitably lead to a fatal outcome in the near future.

*Operation.*—On September 27, 1941, three days after admission, operation was performed (by A. S. W. T.) under cyclopropane-oxygen-ether anaesthesia by a technique previously described.[13] The essential operative findings were as follows: (1) widespread adhesions of the left upper lobe of the lung to the pericardium, mediastinum, and interior of the thorax, anteriorly and laterally, (2) an area of pulmonary infarction, measuring roughly 3 by 3 inches, in the anterior axillary portion of the upper lobe, adjacent to the pericardium, (3) marked cardiac enlargement, (4) a visible tremor and palpable thrill over the base of the heart and pulmonary artery, (5) a greatly dilated pulmonary artery (1¼ inch in diameter), the tenseness of which approximated that of the aorta, (6) intense edema of the mediastinal pleura (1¼ inch thick), and edematous, inflamed lymph nodes at the local site; and (7) an inflamed, indurated ductus arteriosus, approximately ½ inch long and ½ inch in diameter, which was markedly adherent to the surrounding structures, and especially to the upper end of the trunk and right branch of the pulmonary artery.

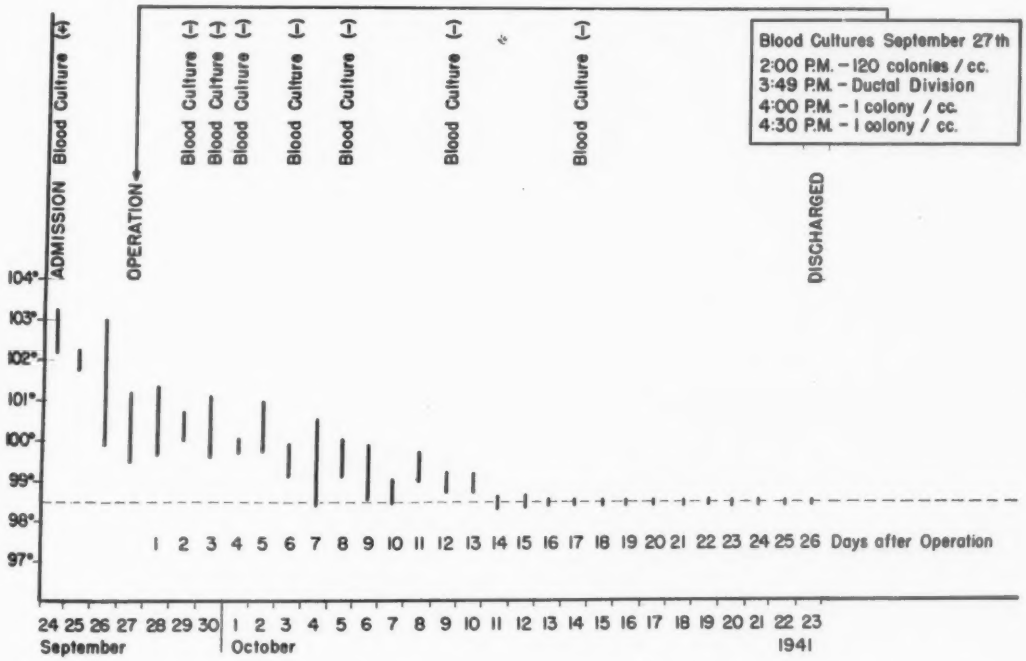
Blood Culture
ADMISSION
OPERATION
Blood Cultures September 27th
2:00 P.M. – 120 colonies / cc.
3:49 P.M. – Ductal Division
4:00 P.M. – 1 colony / cc.
4:30 P.M. – 1 colony / cc.
DISCHARGED
104°
103°
102°
101°
100°
99°
98°
97°
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 Days after Operation
24 25 26 27 28 29 30 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
September
October
1941
J.Z. Case No. 7
NO CHEMOTHERAPY ADMINISTERED POST-OPERATIVELY

Fig. 4.—Clinical chart. Note temperature and blood cultures before and after operation. (Chemotherapy administered without effect, prior to admission to hospital. Chemotherapy not administered, after admission, either pre- or postoperatively.)

Slight bleeding was encountered as the final stage of dissection of the ductus was being completed, and therefore the ductus was doubly clamped and divided completely.* The two clamped ends then were ligated individually with heavy silk. The blood pressure after ligation rose from 118/40 to 150/80.

*The particular operation performed in this case and in Case 1[1] represent the only two such procedures to be reported in the literature thus far.

A blood culture taken during operation, before the ductus was ligated, later was reported to contain 120 colonies of *Streptococcus viridans* per c.c. after 48 hours of incubation. The first postoperative blood culture was taken in the operating room, eleven minutes after actual division of the ductus. This was an arterial specimen (taken from the radial artery). After forty-eight hours of incubation, it contained only one colony of *Streptococcus viridans* per c.c. The second postoperative culture was taken thirty minutes later; it also contained one colony per c.c., after forty-eight hours of incubation.

*Postoperative Course.*—The postoperative course was astonishingly uneventful. The cardiac murmur disappeared at once, and the fever subsided progressively (Fig. 4). Concomitantly, the toxic appearance vanished, and a sense of well-being returned. After a transfusion, the hemoglobin content of the blood rose from 55 per cent to 70 per cent. The patient was permitted out of bed on the ninth postoperative day and regained strength rapidly. The blood pressure quickly became stabilized at a level of approximately 130/90; and, during the postoperative hospital stay, the weight rose from 85 to 92½ pounds.

Fig. 5.—Patient seven and one-half months after operation. Note marked improvement in general physical condition and state of nutrition.

In addition to the two blood cultures which were taken in the operating room after division of the ductus, cultures were taken on the second, third, fourth, sixth, eighth, twelfth, and seventeenth postoperative days. All remained sterile throughout fourteen days of incubation. No chemotherapy was administered at any time.

At the time of discharge, on the twenty-sixth postoperative day, the patient was in excellent general physical condition, her circulatory status was normal, and all clinical and laboratory evidence of subacute *Streptococcus viridans* infection had disappeared. Thirty-six weeks have elapsed since operation. During this period the patient has remained entirely free of symptoms referable to infection and circulatory failure and has gained forty-six pounds in weight (Fig. 5). According to her

parents, she is in better physical condition than at any time since birth. The heart has diminished considerably in size and the previous site of the pulmonary infarct is identifiable only by a small residual shadow (Fig. 6).

*Summary.*—A schoolgirl, aged 18 years, had a patent ductus arteriosus complicated by mild circulatory insufficiency. Subsequently, subacute *Streptococcus viridans* endarteritis developed. She was admitted to a hospital, where intensive chemotherapy for five weeks failed to result in improvement. While she was there, the circulatory involvement increased.

Fig. 6.—Roentgenogram of chest seven months after operation. Note reduction in size of heart. Pulmonic conus is less prominent. Faint shadow adjacent to left cardiac border represents the remains of the previous pulmonary infarct. Pulmonary vascular congestion is still present.

When first observed by the author, she was acutely ill, septic, anemic, and cachectic. Left-sided pulmonary infarction was present. The blood contained as many as 120 colonies of *Streptococcus viridans* per c.c. Although she appeared to be an unusually poor surgical risk, operation was performed promptly in the hope of eliminating infection.

The surgical procedure consisted of division and double ligation of the ductus arteriosus. The blood cultures became sterile promptly after operation, without the use of chemotherapy.

The postoperative course, which was remarkably uneventful, was characterized by rapid disappearance of all manifestations of infection and circulatory involvement. Thirty-six weeks have elapsed since operation and the patient remains entirely well.

## SUMMARY

Subacute *Streptococcus viridans* endarteritis may involve a patent ductus arteriosus at any age.

Under conservative therapy, the disease has proved to be almost invariably fatal.

In the early stages of infection, vegetations are likely to remain confined to the ductus and pulmonary artery. In the latter stages of infection, or even in the early stages of severe infection, vegetations may spread to the cardiac valves or into the aorta. Aortic spread seems to occur chiefly in cases in which the ductus is short.

Eleven patients who had patency of the ductus arteriosus complicated by subacute *Streptococcus viridans* endarteritis were subjected to operation consisting of ligation (9 cases) or division (2 cases) of the ductus. Nine patients survived the operation; two died of operative hemorrhage.

Of the nine survivors, six recovered from infection without benefit of chemotherapy. The remaining three patients did not recover from infection, despite chemotherapy.

Of the six patients who recovered, none presented evidence of preoperative spread of vegetations to the cardiac valves or aorta. They have been followed for periods of three to twenty-nine months; all are well and have had repeatedly negative blood cultures.

Of the three patients who failed to recover from the infection, two presented evidence of vegetative valvular lesions prior to operation. The third was assumed to have vegetations at the aortic end of the ductus. One died of subacute *Streptococcus viridans* endarteritis approximately eight months after operation. The other two are unimproved fourteen and sixteen weeks, respectively, after operation.

Various aspects of infection of a patent ductus arteriosus which have a bearing upon the results of operative treatment are discussed.

A case to illustrate the safety of operating upon even very ill patients is presented.

## CONCLUSIONS

Ligation or division of the ductus, if performed before vegetations have spread to the cardiac valves or aorta, is an effective and safe method of treating subacute *Streptococcus viridans* endarteritis involving a patent ductus arteriosus.

In view of the fact that conservative therapy seldom proves curative, and that the rapidity of spread of vegetations is unpredictable, operation should be undertaken as soon as the diagnosis of superimposed infection has been established.

ADDENDUM

Since preparing this paper, another patient with an infected patent ductus arteriosus has been operated upon. In view of the nature of the infecting organism *(Staphylococcus aureus)* and the severity of the clinical manifestations, the case was considered one of acute, rather than subacute, bacterial endarteritis. The total duration of infection prior to operation was eleven days. Ligation of the ductus, followed by chemotherapy and the administration of Meleney's bacteriophage, proved effective. Thus the series now consists of twelve operative cases, among which there were seven recoveries, three failures, and two operative deaths.

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DISCUSSION ON "PATENCY OF THE DUCTUS ARTERIOSUS IN ADULTS," BY DRS. ANCEL KEYS AND M. J. SHAPIRO, MINNEAPOLIS, MINN., AND "THE RESULTS OF SURGICAL TREATMENT OF PATENCY OF THE DUCTUS ARTERIOSUS COMPLICATED BY SUBACUTE BACTERIAL ENDARTERITIS," BY DR. ARTHUR S. W. TOUROFF, NEW YORK, N. Y.

Dr. Robert L. Levy, New York.—The experiences which Dr. Touroff has related are, indeed, exciting, and represent another forward step in the surgical treatment of heart disease. At the Presbyterian Hospital in New York, Dr. George Humphreys has

ligated a patent ductus in twelve patients and has kindly placed his data at my disposal. There has been no operative mortality. Five of the group showed bacterial invasion of the blood stream. It is to these five patients that I shall refer briefly.

Three of them are cured. The first patient was a child, 12 years old, with staphylococcus sepsis complicating previous ligation of the ductus, which had reopened. The second patient was also a 12-year-old child who developed *Streptococcus viridans* septicemia after measles. In both cases, adequate treatment with one of the sulfonamide drugs was ineffectual. The third patient was a 30-year-old woman who had had a *Streptococcus viridans* infection for several months; the blood had been rendered sterile by chemotherapy shortly before operation. The fourth case was that of a 42-year-old man with an associated septal defect. Ligation was done only last week, so that the result is still uncertain. The invading organism was a nonhemolytic streptococcus.

The fifth patient died of *Streptococcus viridans* sepsis eight weeks after operation. Multiple lesions were suspected before ligation was performed, both because of the physical signs and the occurrence of peripheral emboli. At autopsy, the ductus, which had been apparently patent at operation, was found to be obliterated, and neither at the pulmonic nor at the aortic end were there signs of infection. Large clusters of vegetations clung to a defect in the interventricular septum and others were present on the mitral, aortic, and pulmonic valves. There were infarcts in the spleen, kidneys, and lungs.

In view of the poor prognosis and the small operative risk, it seems fair to conclude that, in the presence of patency of the ductus arteriosus combined with bacterial sepsis, ligation should be carried out. This may be done even when a septal defect or a valvular lesion is suspected, with the hope that the focus of infection lies in the ductus. Operation is sometimes curative when preliminary chemotherapy has failed to sterilize the blood. The occurrence of peripheral emboli, however, lessens the likelihood of a successful result.

DR. M. J. SHAPIRO, Minneapolis.—Three years ago, before this Association, I presented clinical observations in seventeen cases of patency of the ductus arteriosus. These patients had been followed over a period of years. Later we presented observations in twenty-six cases. It was pointed out then that none of our patients had died and none had developed subacute bacterial endarteritis or congestive failure. Three of these patients were later referred for ligation of the ductus. The result in the first two cases was poor. In the first instance, the vessel which was tied was not the patent ductus, for no change occurred after ligation. The second patient died as result of rupture of the duct at operation. In the third case the operation was completely successful.

As a result of this experience, considerable doubt arose as to the advisability of surgical treatment for the remainder of our patients. We, therefore, decided to delay further surgical interference until we could complete two additional studies. The paper just presented by Dr. Keys on patency of the ductus arteriosus in the adult is one of the studies. The other concerns itself with the results of ligation in all patients operated on up to the present time. We have analyzed the available data in all such cases. The results of this analysis are summarized in a slide which I should like to present at this time. Briefly, this slide shows that twenty-six surgeons have operated upon one hundred thirty-seven patients with patency of the ductus arteriosus. One hundred four of these patients had no infection, and thirty-three had subacute bacterial endarteritis. Of the one hundred four uncomplicated cases, the results were completely successful in seventy-eight. In fourteen instances, the continuous murmur persisted after ligation. Six patients died as a result of rupture of the duct at operation. Two patients developed subacute bacterial endarteritis after ligation. Death resulted in one case as a result of wound infection, and, in one case, nothing could be done because there was a direct arteriovenous communication. In three in-

stances a vessel other than the ductus was ligated. A total of nine patients died as a result of operation, which makes the mortality rate less than 10 per cent. Of the thirty-three cases complicated by subacute bacterial endarteritis, operation resulted in complete success in twenty; that is, the temperature returned to normal, the murmur disappeared, and the patient regained normal health. These patients have not been followed long enough to be sure that they are definitely cured. Five died as a result of rupture of the duct at operation, and, in eight instances, the fever persisted in spite of successful ligation. It is a remarkable fact that, in this entire series of one hundred thirty-seven patients, there were only two errors in diagnosis. It appears, therefore, that, in the hands of well-trained surgeons, ligation of the ductus arteriosus can be performed with less than 10 per cent mortality. This rate will certainly decrease as more experience is gained. It seems likely, too, that most patients with patency of the ductus arteriosus complicated by subacute bacterial endarteritis can be cured by surgical interference, especially if the operation is done early. In spite of these very favorable results, we still feel that only those patients on whom a diagnosis of uncomplicated patency of the ductus arteriosus can be made should be operated upon, and then only after definite evidence of early cardiac enlargement or cardiac embarrassment is present. Our point of view may become less conservative after a number of years of follow-up study of the patients who have been operated upon.

I should like to take this opportunity to disagree with Dr. Levy with regard to operating upon patients with patency of the ductus arteriosus complicated by other congenital heart lesions. I do not believe that surgical treatment should be attempted in any case in which there is the slightest doubt about the diagnosis. Simple, uncomplicated patency of the ductus arteriosus, as an isolated lesion, can be diagnosed correctly, and, in my opinion, in only those cases should the ductus be ligated. No patient with cyanosis or with an electrocardiogram which shows right axis deviation should be operated upon. There is good evidence that isolated patency of the ductus arteriosus is not a congenital cardiac lesion at all. It is not a developmental defect in the same sense that all other congenital heart lesions are. It is to be noted that all of us are born with a patent ductus arteriosus.

DR. PAUL D. WHITE, Boston.—Some of you will have known of Dr. Bourne's paper, published in Lancet, October, 1941, concerning recovery in two cases after ligation and chemotherapy of bacterial invasion of a patent ductus arteriosus. You will be interested in the latest word that came from him, a few days ago, saying that he now has five recovered patients out of six treated by this procedure—combination of ligation and chemotherapy—and that the seventh is about to be operated upon.

I would like also to add a conservative note about the incidence of bacterial endarteritis in patency of the ductus arteriosus. It is really a thought of John Hubbard, a colleague of mine in Boston, who has been associated with Dr. Gross during and since the period of the early ductus operations. He believes, and I am in agreement with him in this respect, that we do not yet have accurate statistics about the incidence of subacute endarteritis in patency of the ductus arteriosus. He thinks that the statistics are weighted now by the fact that the patients who have the infection attract more attention, are more likely to be in hospitals, and are more likely to have autopsies performed on them. We still need fuller and more accurate statistical studies of the incidence of bacterial endarteritis complicating patency of the ductus arteriosus.

DR. MAY WILSON, New York.—I think what Dr. White has said is very important. We have not had adequate statistics on the natural risk for a patient with a patent ductus.

In a paper that is now in press, we have attempted to obtain such data. Over a period of twenty-five years we have observed about 132 children who had some congenital cardiac abnormality. Of these, 32 were considered to have a patent ductus.

Upon analyzing the life expectancy, we found that the risk of dying in any year in the first three decades was about 1 chance in 200. Comparing that with the last mortality risk from ligation quoted by Gross as 1 chance in 10, at the moment I would hesitate in advising operation on a well child.

But we must have more statistics. It must be recognized that the present erroneous impression of the risk of subacute bacterial endarteritis in patients with patency of the ductus is based entirely on reported deaths. The living persons with patency of the ductus are not included in those rates.

DR. B. S. OPPENHEIMER, New York.—A few years ago I think most physicians were not very enthusiastic about surgical treatment of heart disease, but since then there are two conditions in which operation seems to be indicated. One is chronic constrictive pericarditis, to which Dr. White has contributed so notably, and the second is patency of the ductus arteriosus, especially when the patient has bacterial endarteritis and positive blood cultures.

Through the courtesy of Dr. Touroff, I saw five of the seven patients whom he reported, and two points struck me particularly. The first was that one of the patients, after successful ligation, had a machinery murmur which was very loud and perfectly evident to everybody. The second point was the rapidity with which the blood was cleared of the *Streptococcus viridans*. That was very striking.

We have had discussions about these points, and, the last time I asked Dr. Touroff about the latter, he thought that the lungs filtered out the *Streptococcus viridans* and this cleared the blood rapidly. In one case the bacteria disappeared from the peripheral blood stream a few minutes after ligation.

I should like to ask him how he explains the persistence of the machinery murmur and the very rapid disappearance of the bacteria from the blood.

In considering the statistics of recovery from *Streptococcus viridans* infections of the heart or arteries, one should remember that the prognosis of such infections is better when the infection is superimposed upon a congenital anomaly than when it involves an acquired lesion.

DR. EMANUEL LIBMAN, New York.—As you realize, it is a notable result that has been achieved by Dr. Touroff.

The whole development of this subject is very interesting. First, great credit is due to Dr. Maude Abbott. Few realize how great her contribution has been. She will become a greater and greater figure as time goes on. When I was first questioned by Dr. Touroff, I applied to Dr. Abbott for certain data. Some had an idea that Dr. Abbott's search for statistical data would be without real value. Actually, when I wrote for information on certain essential points, she promptly sent all the statistical data that were very much needed. It almost looked as if she had made her studies with this operative procedure in mind.

We must give credit to Dr. Robert Gross, who devised the original operative procedure and performed it successfully in cases in which no infection had occurred by way of the ductus.

Then comes the work of Dr. Touroff, who had great enterprise and ingenuity. It was very courageous to attempt to carry out ligation of the ductus in the presence of infection. This was particularly true because in two patients without infection, on whom ligation was done by others, infection of the ductus and pulmonary artery resulted.

Helpful in the advancement of the work have been the diotrast studies which were first made by Robb and Steinberg (I.), and later by Sussman, Steinberg (M. F.), and Grishman. Such studies are absolutely essential in some cases. We have reason to believe that, in the presence of certain congenital cardiac defects, ligation of the ductus may be harmful to the circulation.

My own calculations would seem to indicate that an open ductus is even more frequently present than Dr. Touroff has indicated.

When I encouraged Dr. Touroff to proceed with his operative studies, I did not do so for empirical reasons. Subacute bacterial pulmonary arteritis depends for its development on the infective agent, tension, irregularities of the wall that may be present as a result of tension and, perhaps, thrombi on such irregularities, and the presence of oxygenated blood. We know how little tendency there is for the valves on the right side of the heart to become the seat of subacute bacterial endocarditis. It is believed that this is because of the presence of venous blood and lower pressure. When the ductus is ligated or resected, the high pressure is reduced, and the supply of arterial blood is stopped.

The blood cultures become negative, I believe, because of the great diminution in the force of the current on the vegetations. It must be remembered that, with any source of a bacteremia, even if the focus is radically removed, a few stray bacteria may remain in the blood for a few days. Then one is likely to find them only in cultures made in fluid media.

Dr. Oppenheimer brought up the question as to the mechanism of the murmur in these cases of patency of the ductus. After Dr. Touroff had ligated and sectioned the ductus in the first case, a continuous murmur was still heard, although less marked. When he pressed on the pulmonary artery, the murmur disappeared. We must suspect that the continuous murmur is caused by the passage of blood at high pressure to a dilated pulmonary artery, without tense walls.

Dr. J. W. Wilce, Columbus.—I have never seen or heard of a case such as I want to show you.

This slide shows a team after they had won a championship. One of those boys had patency of the ductus arteriosus. He played for two years with chronically infected tonsils and a patent ductus arteriosus. When he came in on a matter of consultation the third year, it was decided that he should have his tonsils removed, wait six weeks, and after that try half-time work and stop even modified play in case suggestive symptoms were noted.

I am postulating that the ductus shown in the slide is a pretty large and long one. It is a "silent" one, but when one investigates it in the left oblique position, a pulsating connection between the aorta and pulmonary artery is seen. It is possible that the increase in stroke volume that comes with sports was the cause of that dilatation of the patent ductus arteriosus.

Dr. Samuel E. Levine, Boston.—As I see it, there are two therapeutic problems that we are working with: ligation for subacute bacterial endarteritis involving a patent ductus, and ligation of a noninfected ductus.

There cannot be very much argument about the first. We know about the mortality rate of subacute bacterial endarteritis involving a patent ductus. It is extremely high, and the operative risk is becoming less and less. In Boston, Dr. Gross had no deaths in the last thirty cases; other surgeons will do likewise with a little experience and care, perhaps not so much experience, as anatomic knowledge. It is imperative, however, that we make the diagnosis early. We can almost guarantee a cure if the diagnosis is correct and made early, and if we do not wait three months for chemotherapy to be tried. So I don't see that there can be any question about the value of the operation in subacute bacterial endarteritis.

The other question is entirely an open one. It is important to remember what we heard this morning, namely, that the average age at death in fifty or sixty cases of uncomplicated patency of the ductus was only 35 years. Those patients were over 17 years old when first seen; people who are well at 17 years are expected to live to 60 or 70 years. This group lived only to 35 years, and I do not know that we can make any prediction at the age of 18 or 20 years as to which one person is going

to develop subacute endarteritis. Therefore, we must try to find out whether the operation prevents subacute bacterial endarteritis. If so, the mortality risk of surgical treatment is a great deal better than letting the person live his life expectancy, which averages 35 years. The question we have to keep in mind is: Will the operation prevent subacute bacterial endarteritis? It certainly will prevent subsequent heart failure if that is the only lesion.

DR. ARTHUR S. W. TOUROFF, New York.—I am happy to hear from Dr. Levy and Dr. White that the work which I have presented has already been confirmed by other investigators.

In answer to Dr. White and Dr. Wilson, I would like to emphasize that my presentation deals only with the treatment of patency of the ductus arteriosus which is already complicated by subacute bacterial endarteritis. Under the circumstances, the actual incidence of subacute bacterial endarteritis as a complication of patency of the ductus does not concern us here, for the reason that we are not discussing the value of operation as a prophylactic procedure in the prevention of infection. To the patient who has already developed subacute bacterial endarteritis, the incidence of this complication is 100 per cent. Thus, we are not operating to prevent infection, but are treating patients who already have infection.

By way of discussion of Dr. Wilson's statements, if a group of normal children have a certain life expectancy, it seems logical to assume that those with a patent ductus who are threatened by cardiac failure and subacute bacterial endarteritis have a shorter expectancy of life. In this connection I would again like to point out that cardiac failure may develop late in life, and that subacute bacterial endarteritis occurs more commonly in adults than in children. Thus if we use the age criterion of Drs. Keys and Shapiro, we find that infection occurred during childhood in only one of our eleven cases.

In answer to Dr. Oppenheimer, it is to be emphasized that a continuous machinery murmur persisted after operation only in the first case. Since the ductus was divided completely, recanalization could not have occurred. When the case was reported originally, I drew attention to the fact that, during operation, the murmur became less intense, but did not disappear until the pulmonary artery was temporarily compressed. This seemed to indicate that the murmur was generated within the latter vessel. Several of the other patients had residual, soft, systolic murmurs which are gradually becoming less intense.

Time does not permit discussion of the mechanism of recovery, but I believe that operation is effectual chiefly because it corrects certain abnormal mechanical factors. This subject will be presented in a separate paper.

In conclusion, I urge that operation be performed promptly upon all patients who have developed infection.

DR. ANCEL KEYS, Minneapolis.—In connection with the recurrence or persistence of a murmur in some cases after ligation, I should like to point out that we have evidence that there may be an open ductus with no murmur, but there is no proof that we may have a murmur with the ductus closed. Duroziez, in 1862, reported a case of patency of the ductus arteriosus (diagnosis substantiated at autopsy), in which there was no murmur of any kind, and we have recently had a similar case, likewise with autopsy. In both of these instances the pulmonary artery was enlarged, so that we should have expected murmurs if the murmur of a patent ductus is primarily a result of pulmonary enlargement. Further, we know that, in at least one instance in which a murmur recurred after ligation, there had been, in fact, reestablishment of communication between the aorta and pulmonary artery. Unless some really valid evidence to the contrary is presented, I believe we must assume that persistence or recurrence of the murmur after attempted ligation indicates persistence or recurrence of the aorta-pulmonary artery communication.

# A PHYSIOLOGIC DEFINITION OF ACUTE CONGESTIVE HEART MUSCLE FAILURE

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THERE is urgent need for an accurate quantitative definition of acute congestive heart muscle failure in physiologic terms. Such a definition should contain magnitudes which are not only capable of measurement in animal experiments, but which may be fairly accurately ascertained in measurements on patients with heart failure before and after treatment. In this paper we shall prove through animal experiments that decreased mechanical efficiency* is the basic factor in acute congestive heart failure. Papers in which this viewpoint will be established by investigations already carried out on man will appear shortly.

In 1912, Knowlton and Starling[1] devised the heart-lung preparation, and, in making use of this preparation, they showed that the ability of the mammalian heart to do work is a function of the diastolic length of the heart muscle fibers, or diastolic volume. In other words, if the heart is to do more work per beat either by increasing the stroke output or the mean blood pressure or both, it must dilate. In his Linacre Lecture on the law of the heart, Starling[2] stated that the failing heart produces less external work at a constant diastolic volume. Here we already have an accurate definition of heart muscle failure. This definition could be improved only if we knew the relationship of diastolic volume to total energy release per beat.†

Shortly after Starling devised his heart-lung preparation, Socin,[3] in 1915, working in the physiologic laboratory of Magnus, in Utrecht, and Bijlsma and Roessingh,[4] in 1922, carried out experimental investigations of acute cardiac weakness as produced by chloroform and chloral hydrate on the heart in a heart-lung preparation. They showed that chloroform and chloral hydrate produced dilatation of the heart, a decrease in cardiac output, and a decrease in average blood pressure, thus confirming Starling's statement that a failing heart does less work at a given diastolic volume. Starling tended to minimize the factor of increase in venous pressure when the heart dilates because of his conviction that it was the diastolic length of the heart muscle fibers that determined the work of the heart. On the other hand, every cardiologist

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*The ratio of work performed to the oxygen consumed in releasing energy from fuel materials is the mechanical efficiency of a machine.

†Total energy release = heat produced plus work performed.

is aware that the cardinal symptoms of heart failure, namely, dyspnea and dependent edema, are largely the result of a rise in venous pressure. On repeating these experiments, making use of chloroform and chloral hydrate to produce a hypodynamic heart muscle in heart-lung preparations, one of us (G. F.) noted that the venous pressure always rises at the same time that the heart dilates, and that the mean blood pressure could be held constant.* There is usually some decrease in cardiac output, also, but this may be very slight with moderate degrees of poisoning. In our teaching we then made dilatation and rise in venous pressure the criteria of heart failure.

Starling and Visscher[5] showed that the oxygen consumption of the heart increased when the diastolic volume or length of the muscle fibers increased. Decherd and Visscher[11] found that the work of the turtle heart decreased during spontaneous failure when the diastolic volume, and, therefore, the oxygen consumption, were held constant. Peters and Visscher[6] showed that the ratio of the work performed by the spontaneously failing heart to the oxygen consumption of that heart increased when ouabain and scillaren-B were added to the blood circulating in the heart-lung preparation. A little later, Visscher and Moe[7] proved that a digitalis glycoside, digilanid C (cedilanid), also increases the mechanical efficiency of the spontaneously failing heart. The experiments of Starling, Visscher, Peters, and Moe make it appear that a decrease in mechanical efficiency is the most likely cause of acute heart failure.

A search through the literature unearthed only one paper (with the exception of the papers from Visscher's laboratory, quoted above) in which an attempt was made to measure the diastolic size of the heart, the venous pressure, and the mechanical efficiency of the heart during spontaneous failure. In 1938, Katz and Mendlowitz[8] published an analysis of spontaneous heart failure in the isolated heart circuit. They measured the diastolic size of the heart by means of either calipers or an oncometer. By obtaining arterial blood samples from the outflow system of the left side of the heart and venous blood from a glass cannula passed into the coronary sinus, they assumed they could calculate the oxygen consumption of the heart. In the summary of their paper, they stated that with their preparation it was possible to permit failure to occur with little or no change in total diastolic volume. They found that under these circumstances there was a progressive decrease in the work and oxygen consumption of the heart, and little change in its mechanical efficiency. They concluded that "when the work of the heart was kept constant, no change in oxygen consumption or mechanical efficiency occurred, despite a progressive increase in the diastolic volume and the left auricular pressure." They also concluded that failure of a heart chamber is caused by an increase in load or decrease in contractile power, or both, of such a degree that the chamber begins to fail to do the

*Unpublished experiments.

work imposed upon it by the load. They also state as a conclusion "that loss of contractile power is manifested by a reduction in total energy release, and hence work at a given diastolic volume and (except terminally) not by a decrease with which the liberated energy is utilized for mechanical work." The work of Katz and Mendlowitz cannot be considered as proving their conclusion because their measurements of oxygen consumption did not take into account the oxygen consumption of the blood that returned to the right side of the heart via Thebesian channels; it has been shown that the oxygen content of this blood may differ very greatly from that of the blood in the coronary sinus.[9] Moreover, there is a discrepancy in their conclusions. They speak of heart failure in conjunction with little or no change in total diastolic volume in one statement, and, in another, they mention a progressive increase in the diastolic volume. Their one curve showing diastolic volume indicates a progressive increase in the volume. Katz and Mendlowitz state in their paper that it is apparent that loss of mechanical efficiency is not an essential factor in heart failure, and that such a loss does not occur except as a terminal event. We will show later that this statement is not true.

Since one of the poisons with which we did our work was diphtheria toxin, we wish to review the work of Witt, Lindner, and Katz,[10] who studied the effects of acute experimental poisoning of the heart with diphtheria toxin. They made use of the intact dog, so that their work not only shows the effect of diphtheria toxin upon the myocardium, but also upon the peripheral circulation. Under the conditions of their experiments, the stroke volume declined. They also state that there was distention of the heart. Their two published curves show at times a rise, and, at other times, a decrease in the diastolic pressure in the left ventricle (venous pressure) during the poisoning. In our opinion, this is because they were dealing with a combination of heart failure and peripheral vascular failure. We can find no measurements of stroke or minute output, and no quantitative data on changes in the diastolic volume of the heart. Among other things, they observed various cardiac arrhythmias which could have been produced by diphtheria toxin. Because of the complications in the experiments of Witt, Lindner, and Katz, we do not believe that this work can be accepted as the final word regarding the effect of diphtheria toxin on the myocardium itself.

Our search of the literature convinced us that there was a place for renewed investigation of the physiologic factors of diastolic volume, mechanical efficiency, venous pressure, cardiac output, and blood pressure when the heart is made hypodynamic by the administration of cardiac poisons.

An experiment to ascertain the effect of cardiac poisons on the function of the mammalian heart muscle should be carried out only on the isolated heart-lung preparation or an isolated heart with a mechanical

oxygenator taking over the function of the lung, because, otherwise, peripheral vascular factors will mask or complicate the results of the heart muscle failure. Because of our many years of experience with the Starling heart-lung preparation, we selected this method. Later we added the Visscher oxygen consumption apparatus. As cardiac poisons, we selected chloral hydrate, chloroform, diphtheria toxin, alcohol, and potassium chloride. Fig. 1 is a schema of the heart-lung preparation as used by us. It is essentially a heart connected to the pulmonary circulation with the lungs intact, with an artificial resistance, which can be varied to suit the desires of the experimenter, inserted into the arterial circulation. This circulation consists of a glass cannula in the brachio-

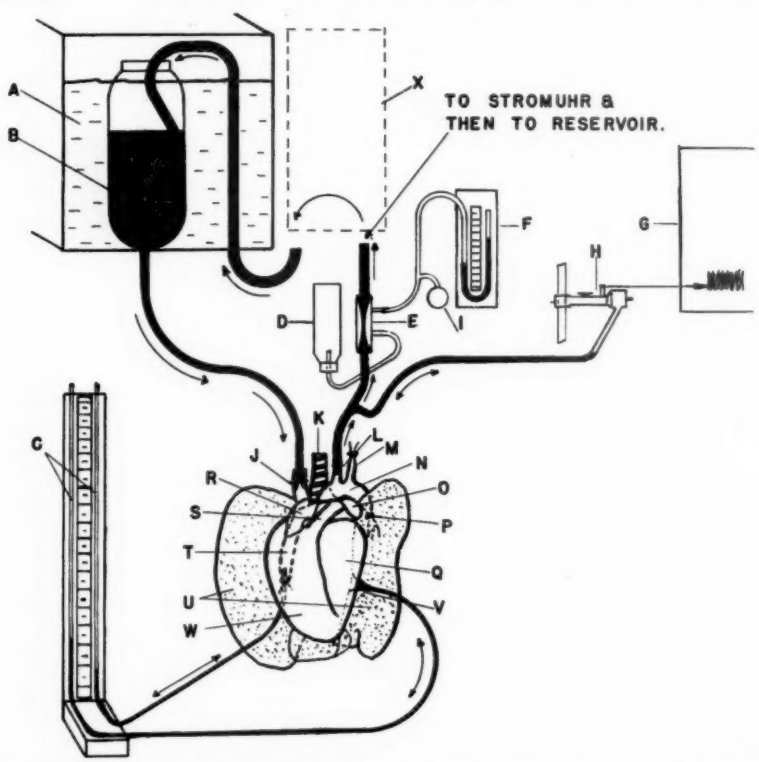


Fig. 1.—*A*, Constant temperature bath; *B*, blood reservoir; *C*, venous pressure manometer; *D*, bottle used as air cushion for peripheral resistance chamber; *E*, peripheral resistance chamber; *F*, mercury manometer; *G*, kymograph; *H*, Straub blood pressure manometer; *I*, pressure bulb; *J*, superior vena cava and cannula; *K*, trachea; *L*, brachiocephalic artery and cannula; *M*, ligated subclavian artery; *N*, arch of aorta; *O*, left auricle; *P*, ligated aortic arch; *Q*, left ventricle; *R*, right auricle; *S*, pulmonary artery; *T*, inferior vena cava and cannula; *U*, lungs; *V*, small cannulated pulmonary vein; *W*, right ventricle; *X*, position where stromuhr stands.

cephalic artery of the dog and a series of glass and rubber tubes carrying the blood pumped out of the heart up to the venous reservoir, which is itself connected to the superior vena cava by rubber tubing and a glass cannula (Fig. 1). All of the branches of the root of the aorta, except the brachiocephalic artery, are ligated, and the aorta itself is ligated just beyond the brachiocephalic artery. Thus the only part of

the systemic circulation which remains intact is the root of the aorta. The lungs are ventilated by means of a pump, so that the heart-lung preparation is kept well oxygenated. In the heart-lung preparation as we used it for this experiment, one water manometer was connected to the inferior vena cava in order to measure the right auricular pressure, and another was connected with a branch of the pulmonary vein in order to measure the left auricular pressure. A cardiometer, fitted around the auriculoventricular groove, was connected to a large tambour in order to record changes in the diastolic and systolic volume of the ventricles. At the beginning and end of each experiment the cardiometer was calibrated by noting the excursions of the tambour level after injections of 20 c.c. quantities of air into the cardiometer system. It was thus possible to measure dilatation of the ventricles in cubic centimeters. A cannula, connected to a Straub membrane manometer, was inserted into the arterial circulation near the brachiocephalic artery, and a Stolnykow stromuhr for measuring minute output of the heart was connected to the arterial circulation just beyond the artificial resistance. The venous reservoir was kept at constant temperature by a water bath which was heated and stirred electrically. A device connected to the heating element kept the temperature constant within 0.1° C. A screw clamp, connected to the rubber tubing leading from the venous reservoir to the cannula in the superior vena cava, regulated the rate of volume inflow into the right auricle.

It has been our experience that the artificial resistance keeps the arterial diastolic pressure nearly constant at the desired level throughout great changes in the conditions of the experiment. The systolic blood pressure varies with the stroke output of the heart. There is easy access to the venous reservoir, so that cardiac poisons or digitalis glycosides can be inserted readily. The minute volume is measured by observing the time (with a stop watch) required for the blood to flow from one mark on the stromuhr to another mark; the volume between the two marks is 50 c.c. The stop watch measures one-fifth of a second. The error of the measurement of minute volume is determined by this one-fifth second scale division. The rate of the heart is largely controlled by the temperature in this preparation, so that the heart rate remains constant over a large range of changes. Cardiac poisons may cause heart block, extrasystoles, and auricular fibrillation, all of which may alter the ventricular rate; otherwise the rate of the ventricles is constant.

When we measured oxygen consumption, we made use of the heart-lung preparation in the oxygen consumption apparatus, as devised by Dr. Visscher.[6] In this case we used the apparatus in Dr. Visscher's laboratory and had the advantage of his advice, as well as that of Dr. Lorber, an assistant in his department. If proper precautions are taken, the results obtained with this apparatus are accurate. The clinician will note that this method of measuring oxygen consumption is an adapta-

tion of the one which he uses in estimating the basal metabolic rate; the adaptation is made to the trachea of the heart-lung preparation rather than to the mouth of the patient. A pump is inserted in the apparatus to keep the oxygen circulating into the lung during the inspiratory stroke and out of the lung and into the spirometer when the stroke of the pump is in the opposite direction. Fig. 2 is Dr. Visscher's schema of this apparatus. We will not go into a discussion of its accuracy; this has been done by Dr. Visscher, and a critical reader can look it up in his papers. Let it be said that the results obtained with this oxygen consumption apparatus have been checked with those obtained with an isolated heart and mechanical oxygenating apparatus and found to be accurate if the proper precautions are taken.

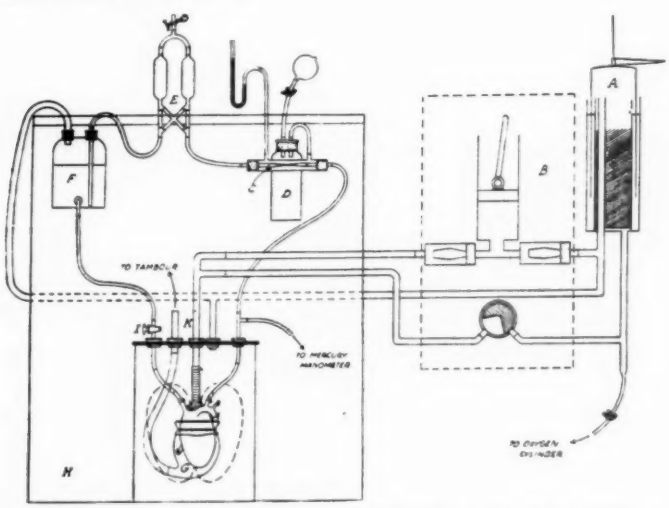


Fig. 1.—*A*, oxygen spirometer; *B*, respiration pump; *C*, artificial resistance; *D*, pressure bottle; *E*, Stromuhr; *F*, venous reservoir; *G*, cardiometer; *H*, constant temperature bath; *I*, stopcock for adjustment of venous return; *K*, tracheal cannula.

Fig. 2.—Schematic drawing of the Visscher heart-lung oxygen consumption apparatus. This is a photograph of Fig. 1 from the paper by Peters and Visscher, The Energy Metabolism of the Heart in Failure and the Influence of Drugs Upon It, AM. HEART J. 2: 273, 1936. Dr. Visscher's permission was obtained for the use of this figure.

In the course of this investigation we repeated the original experiments of Starling upon which the law of the heart was based. In Fig. 3 we show the effect of increasing the venous return to the heart. Starting with a volume flow of 50 c.c. in 11.2 seconds in the arterial system, or a minute volume of 270 c.c. per minute if we neglect the coronary flow, we observed that the venous pressure in the pulmonary vein on the left side was 3.3 cm., and, on the right side, or in the inferior vena cava, was 2.8 cm. of water. The blood pressure was 105/95. Now the inflow from the venous reservoir was increased by taking off some of the pressure on the clamp constricting the tube running from the reservoir to the superior vena cava. The flow immediately increased until 50 c.c. were injected from the left ventricle into the arterial system in 2.8 seconds,

which gave a minute output of 1070 c.c., neglecting the coronary flow. The blood pressure at this time was 117/91. The venous pressure went up on the left to 9.5 cm., and, on the right, to 8.7 cm. At the same time the heart dilated 25 c.c. in diastolic volume. The inflow from the venous reservoir was now decreased until it took 5.6 seconds to eject 50 c.c. from the left ventricle into the arterial system, giving a cardiac output of 535 c.c. per minute if we neglect coronary flow. The blood pressure at this time was 112/95. The venous pressure went down to 5.0 on the left and 4.5 on the right, and the dilatation of the heart receded 18 c.c.

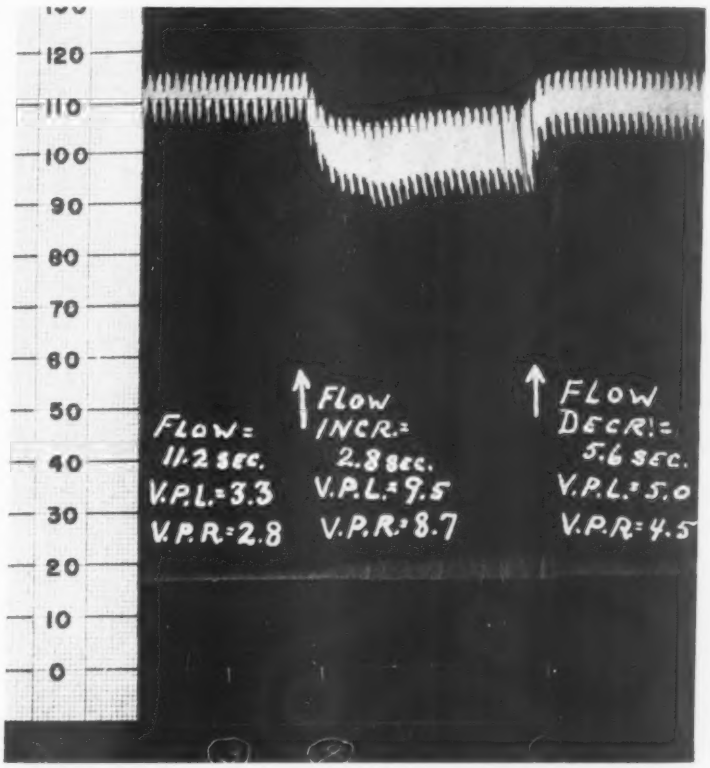


Fig. 3.—Influence of cardiac output on the diastolic volume of the heart and on the venous pressure. Top curve is cardiometer tracing, systole up, diastole down. Dilatation is represented by a downward displacement of the curve. Blood pressure curve (Straub manometer) below cardiometer tracing. "Flow" means the number of seconds during which 50 c.c. of blood flowed from the left ventricle into the aortic system, as measured in the flow meter. This amount is exclusive of the amount flowing into the coronary system. VPL = venous pressure on the left in cm. of water. VPR = venous pressure on the right in cm. of water. The dilatation of these ventricles was 25 c.c. in going from a minute flow of 270 c.c. to a minute flow of 1,070 c.c.

At the end of this experiment we tied off the two ventricles just beyond the cardiometer and measured their volume with the contained blood. This volume was 120 c.c. The weight of the ventricles without the blood was 97 grams. From data published in the thesis of Hymer L. Friedell, "The Estimation of the Size and Stroke Output of the Heart by Means of Roentgenkymography," submitted to the University of

Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy, as well as from data obtained by roentgenkymography on the hearts of two internes at the Minneapolis General Hospital, we calculated that the diastolic volume of the heart of a man 170 cm. in height and weighing 70 kilos is approximately 600 c.c. The diastolic volume of this average man's heart would increase by 125 c.c. under the same conditions that cause the 25 c.c. dilatation in our dog's heart, assuming that the diastolic volume of the auricles enlarges proportionately with that of the ventricles. From data obtained by roentgenkymography on the two internes' hearts we have calculated that the enlargement of

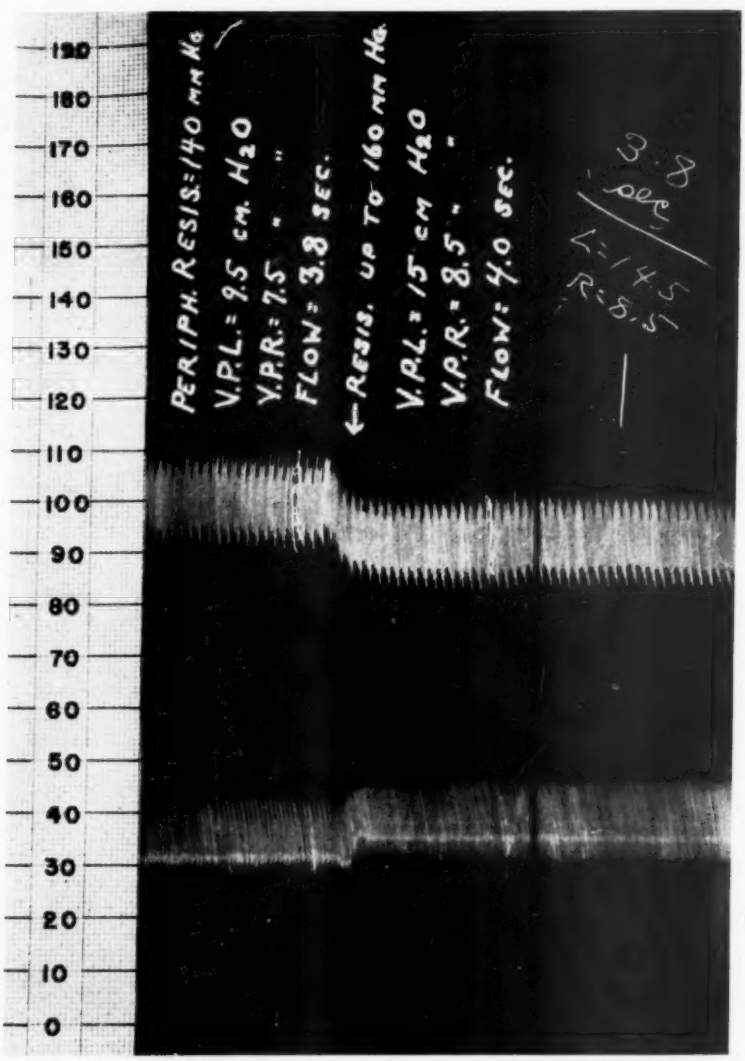


Fig. 4*a*.—Influence of blood pressure increase on the diastolic volume of the heart and the venous pressure. Peripheral resistance is the pressure under which the artificial resistance in the heart-lung apparatus was placed. VPL = venous pressure on the left in cm. of water. VPR = venous pressure on the right in cm. of water. Flow is number of seconds needed for 50 c.c. of blood to pass from the left ventricle into the aortic system, exclusive of the amount flowing into the coronary arteries.

the transverse diameter of this normal heart would be approximately 7 mm. if the increase in diastolic volume was 125 c.c. These data give us the order of magnitude of the increase that would take place in the diastolic volume and transverse diameter of a normal sized human heart if its work per beat were increased approximately four times by increasing the stroke output four times. We have repeated this type of experiment many times in the course of this investigation and the result has always been the same. Increasing the work of the heart by increasing its output always causes dilatation of the heart, and, at the same time, there is an increase in the venous pressure in both the left and right auricles.

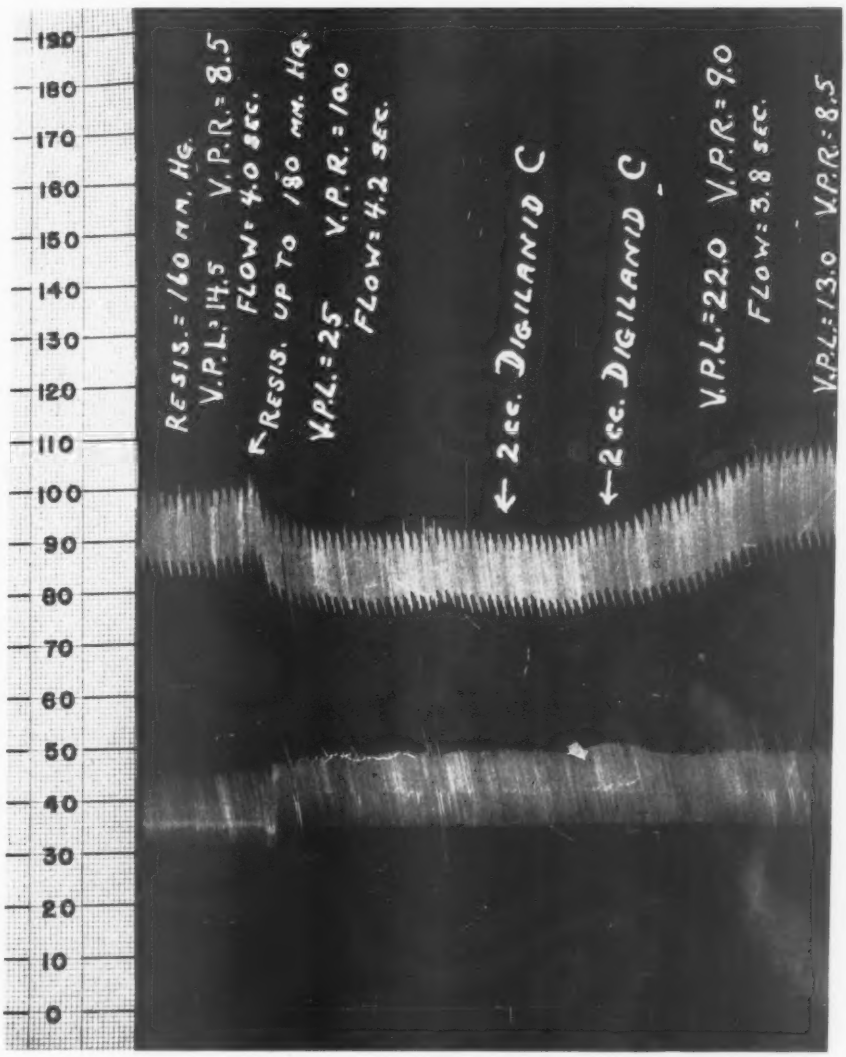


Fig. 4*b*.—Continuation of 4*a*. Another increase in peripheral resistance was brought about at the point marked by the arrow. Four c.c. of digilanid C were introduced at point marked on curve.

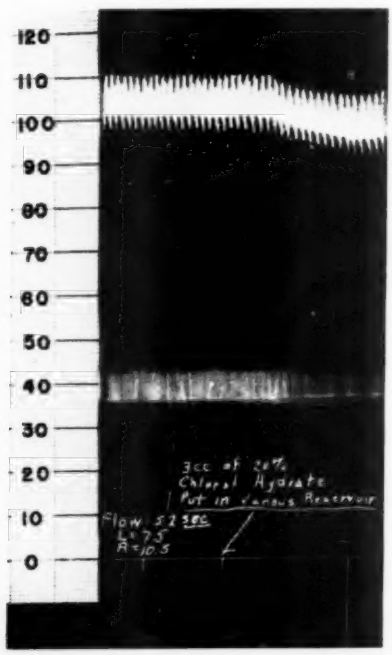


Fig. 5*a*.—Experiment with chloral hydrate. Upper curve, cardiometer tracing. Next curve below this, blood pressure record of Straub manometer. *L* is the venous pressure on the left. *R* is the venous pressure on the right.

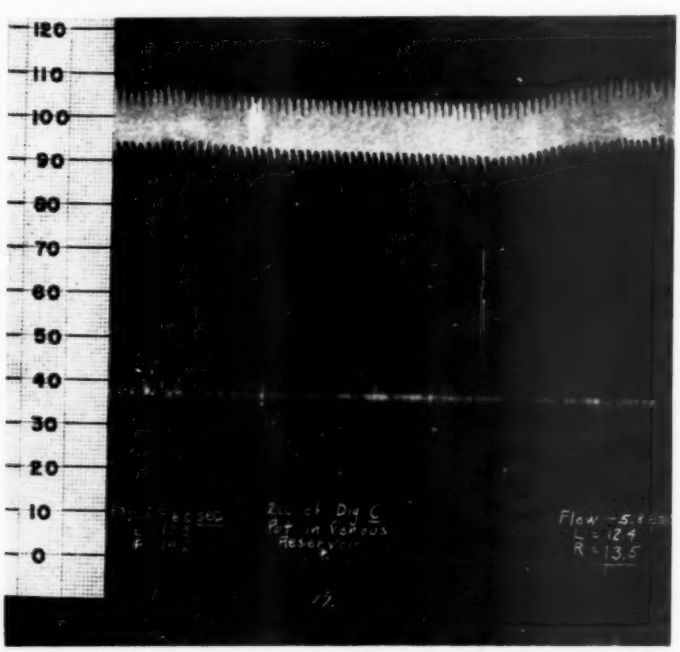


Fig. 5*b*.—Continuation of 5*a*. One and one-half cubic centimeters of 20 per cent chloral hydrate solution have again been added, and continuous dilatation takes place. At the point marked on the signal curve, 2 c.c. of digilanid C were put into the reservoir, effecting decrease in diastolic volume, increasing the rate of flow, and decreasing the venous pressure.

Fig. 4a shows the effect of increasing the artificial peripheral resistance from 140 to 160 mm. Hg. The blood pressure increased from 190/144 to 210/162 mm. Hg. The minute volume, as measured by the flow meter in the arterial system, dropped from 790 c.c. to 750 c.c., a difference which depends largely upon increased flow in the coronary system caused by the rise in mean arterial pressure. The stroke output, as measured by the difference between the systolic and diastolic volumes on the cardiometer record, showed no measurable change. The ventricles dilated 8 c.c., and the venous pressure went up from 9.5 c.c. to 15 cm. of water in the left auricle and from 5.5 cm. to 8.5 cm. of water in the right auricle. Fig. 4b shows the effect of further increasing the artificial resistance to 180. The blood pressure rose to 223/187, and the heart di-

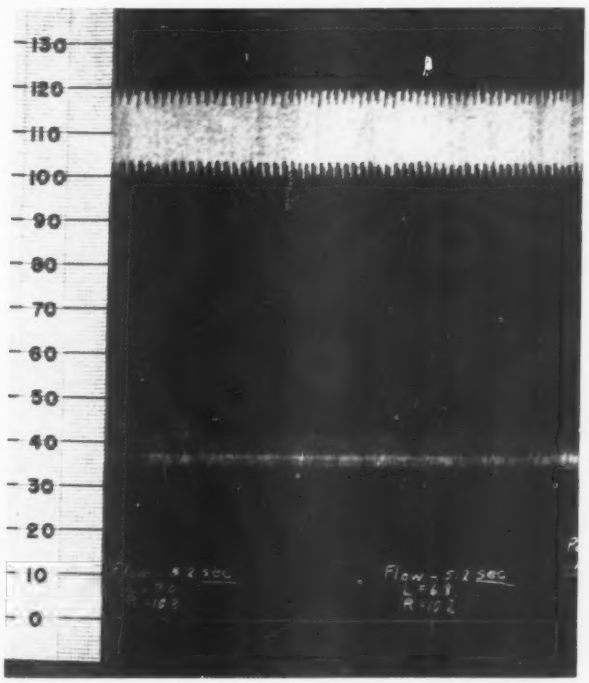


Fig. 5c.—Continuation of 5*b*. Continued effect of digitalis, reducing the diastolic volume to normal and bringing back the velocity of flow in the aorta to the original level.

lated another 8 c.c. The venous pressure went up to 25 cm. on the left and 10 on the right. The minute output, as measured by the stromuhr, fell to 715 c.c. per minute. The difference between 790 and 715 c.c. per minute was largely the result of the increase in flow in the coronary system caused by the increased mean blood pressure. The difference between the systolic and diastolic volumes on the cardiometer tracing showed no measurable change in stroke output. Rises in blood pressure in a good heart-lung preparation are not accompanied by a fall in cardiac output.

Four c.c. of digilanid C were then introduced into the reservoir, and, within a short period of time, with the blood pressure remaining at 227/179, the venous pressure started to fall and the output to increase. At the end of the curve the venous pressure had declined on the left to 13, and, on the right, to 8.5 cm. of water, and the minute volume had increased to 790 c.c. At the same time the diastolic volume had decreased 15 c.c. Two minutes later the venous pressure had come down to 8.8 cm. on the left and 7.5 cm. on the right, and the minute volume had increased to 835 c.c. This digitalis effect indicates that considerable spontaneous heart failure was present, despite which the Starling "law of the heart" held good.

Figs. 5a, b, and c illustrate well an experiment in which chloral hydrate was used to produce failure of the dog's heart. Before the chloral hydrate was given, the venous pressure on the left was 7.5, and, on the right, was 10.5. The minute volume of flow through the flow meter was 575 c.c. per minute. The blood pressure was 125/92. At the point marked by the arrow, 3 c.c. of a 20 per cent solution of chloral hydrate were put into the venous reservoir; the latter contained approximately 1000 c.c. of blood. Within a minute after introducing the chloral hydrate the heart had dilated 7 c.c. and the venous pressure had risen to 10.3 on the left and 12.3 on the right. At the same time the cardiac output, as measured by the stromuhr, had fallen to 540 c.c. per minute, and the blood pressure was 122/92. A little later, 1.5 c.c. of a 20 per cent solution of chloral hydrate were introduced into the reservoir, and the venous pressure on the left rose to 13.5 and on the right to 14.2. At the same time the diastolic volume of the heart increased 2 c.c. more, the flow decreased to 500 c.c. per minute, and the blood pressure was 115/90. This is illustrated in the first part of Fig. 5b. If we had increased the input into the right auricle so as to bring the work of the heart back to its original value, the dilatation would have increased even more and the venous pressure would have risen higher. As it was, the heart was performing less work at a greater diastolic volume and with an increased venous pressure. At the point marked with a small arrow, 2 c.c. (0.4 mg.) of digilanid C were put into the venous reservoir, and, within one minute, the heart had decreased 4 c.c. in diastolic volume, as illustrated on the curve, and the venous pressure had dropped to 12.4 on the left and 13.5 on the right. At the same time the minute volume in the stromuhr had gone up to 520 c.c. Two c.c. more of digilanid C were now put into the venous reservoir, and, approximately 15 minutes after the first digilanid had been introduced, the diastolic volume of the heart was 5 c.c. smaller than at the beginning of the experiment, as shown in Fig. 5c. The venous pressure on the left was back to the normal of 6.8, and, on the right, to 10.2. The minute volume was, as originally, 575, and the blood pressure was 125/93. This experiment, making use of chloral hydrate to produce a hypodynamic heart muscle, was repeated a number of times on a number of dogs' hearts and the results were al-

ways the same. Chloral hydrate produced dilatation of the heart and an increase in venous pressure. There was some tendency to decreased stroke output, so that the work of the heart decreased. Digitalis tended to bring back the venous pressure to the normal, to decrease the diastolic volume to normal, and to increase the output to the original amount per beat.

A close examination of the cardiometer record during heart failure shows how the changes associated with heart failure are brought about. As the heart failure starts to manifest itself, we note that there is a slight increase in the systolic volume of the heart, indicating that the heart is emptying itself a little less each beat, or, in other words, that the stroke output has slightly decreased. The stroke output continues to decrease, but sooner or later seems to become stationary. In the meantime, the diastolic volume has increased because a greater amount of blood is retained in the ventricle at the end of systole and nearly the same amount comes in from the venous reservoir during the succeeding diastolic period. Therefore, the total diastolic volume increases somewhat. Decrease in the systolic output and increase in the diastolic volume may continue until the heart stops beating, but, as a rule, a point is reached at which the diastolic volume does not increase or increases only very slowly. The systolic volume may now decrease somewhat; in other words, the systolic output may increase until the original level is reached or nearly reached. In severer degrees of poisoning the original stroke output is never reached despite the diastolic volume increase. In the meantime, the venous pressure has increased on both the left and the right side of the heart. A more or less steady state is now achieved, in which, with an increased diastolic volume and an increased venous pressure, the stroke output has increased either to the original value or possibly is a little below it. The mechanism of the increase in diastolic volume is to be found in the decreased systolic output once the poison has produced a hypodynamic state of the heart muscle. The retained blood, plus the blood flowing in from the venous reservoir, tends to increase the diastolic volume. At the same time the venous pressure rises because there is some slowing up of the flow from the venous reservoir into the heart. If the venous pressure did not rise somewhat, the diastolic volume could not increase. In order to get an increase in diastolic volume it is necessary to increase the initial (diastolic) tension on the cardiac muscle fibers.

One of our many experiments with chloral hydrate as a cardiac poison has some additional points of interest to the clinician, in that both asystole and auricular fibrillation were produced, and the administration of a digitalis glycoside, digilanid C, apparently resulted in restoration of normal rhythm. This heart had been experimented upon for about one-half hour before starting the chloral hydrate. At the start of the experiment with chloral hydrate, the blood pressure was 147/127, the cardiac

output was 580 c.c., neglecting the coronary flow, and the venous pressure on the left was 8.2 and on the right 6 cm. Two portions of 2 c.c. each of a 10 per cent solution of chloral hydrate were introduced into the venous reservoir; this caused an increase of about 20 c.c. in the diastolic volume of the heart and a fall in the minute output, as measured by the stromuhr, to 500 c.c. per minute, and the blood pressure fell to 136/116. Four c.c. of a 10 per cent solution of chloral hydrate were then added to the venous reservoir, and within one and one-half minutes the heart

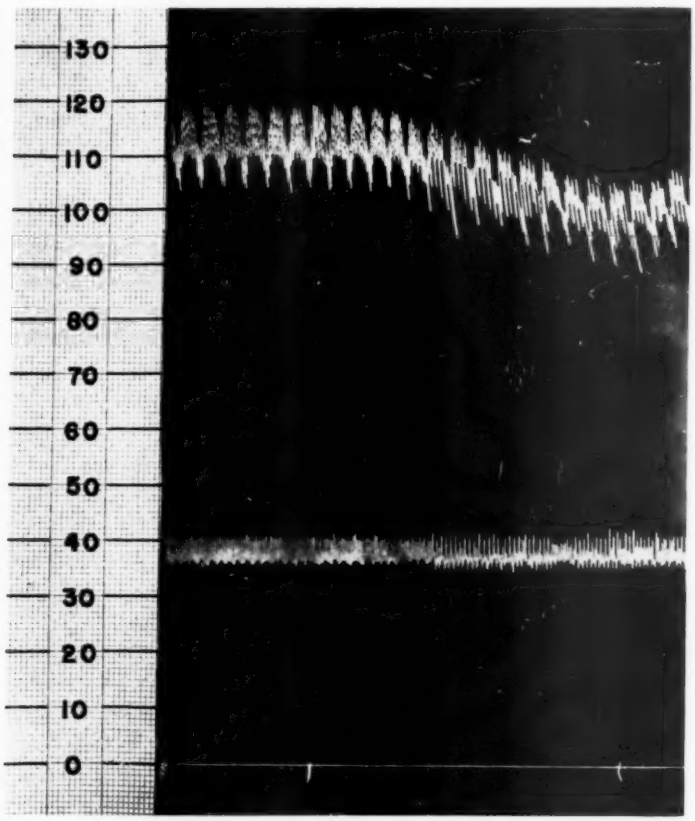


Fig. 6*a*.—Effect of diphtheria toxin on the heart size. At the point marked 6 on the signal magnet, diphtheria toxin was introduced. At the point marked 7 on the signal magnet, velocity of blood flow in the aorta and venous pressure and diastolic volume increase were measured.

started to dilate greatly, the rate of the heart to slow appreciably, and the venous pressures to rise markedly. In a very short time the heart stopped beating, at which time the diastolic volume had increased 65 c.c. more and the venous pressures both on the left and right were 42 cm. of water; this was the height of the venous reservoir above the right auricle. The heart stopped beating for only a few seconds, and then occasional beats appeared. As the heart started to beat again the dilatation receded until there was a total increase of 40 c.c. in diastolic volume

above that before any chloral hydrate had been given. The venous pressure was 20 on the left and 10 on the right. When auricular fibrillation set in, the heart dilated about 44 c.c. again. The venous pressure then rose to 40 on the left and 36 on the right, and the minute output was so slight that it was impossible to measure it accurately. At the point of greatest dilatation, 4 c.c. (0.8 mg.) of digilanid C were given. After four minutes the heart became regular and the dilatation receded until the diastolic volume of the ventricles was back to its original value. The venous pressure finally became 10 on the left and 6 on the right. Analysis

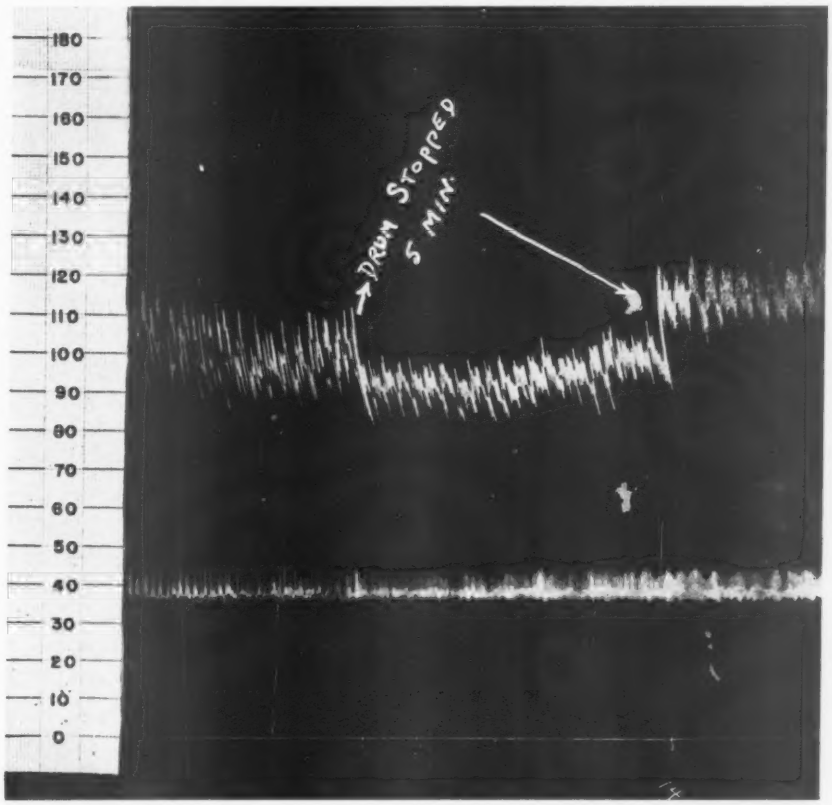


Fig. 6*b*.—Continuation of 6*a*. Continued dilatation of the heart under the influence of diphtheria toxin; marked irregularity. At the point marked 13 on the signal magnet, digilanid C was introduced, with consequent decrease in the diastolic volume of the heart.

of these results shows again that the effect of chloral hydrate as a cardiac poison is to cause a rise in venous pressure, dilatation of heart, and decrease in cardiac output. Chloral hydrate may result in asystole, from which the heart may recover. Auricular fibrillation may then develop, with an increased dilatation of the heart and an increase in venous pressure. Digilanid C may stop the auricular fibrillation, after which the diastolic volume may come back nearly to normal, the venous pressures

may be restored approximately to normal, and the cardiac output may become the same as before chloral hydrate was given.

We carried out three experiments in which diphtheria toxin was used to poison the heart. Two of these experiments were done with the heart-lung preparation without the oxygen consumption attachment, and one was carried out with the oxygen consumption apparatus. It is necessary to use very strong diphtheria toxin in order to produce heart failure within the short period of time necessary for these experiments. These strong solutions of diphtheria toxin tend to produce disturbances such as heart block, extrasystoles, auricular fibrillation, and pulsus alternans. These abnormalities make it very difficult to compute the work of the heart accurately because of the irregularity in the blood pressure.

Fig. 6a shows the cardiometer and blood pressure record in an experiment with diphtheria toxin (L+ = .0092) obtained from the Eli Lilly Company by Dr. Larson of the Department of Bacteriology at the University of Minnesota. At the start of the experiment the minute output was 790 c.c., neglecting the coronary flow, and the venous pressure on the left was 10.2, and, on the right, 10.3 cm. of water. The blood pressure was 127/109. Twenty-four c.c. of the diphtheria toxin were injected into the reservoir, which contained approximately 1000 c.c. of blood. As this seemed to have only a slight effect on the venous pressure and the size of the heart, within 1¾ minutes we added another 16 c.c. Within 45 seconds after this second dose of diphtheria toxin, the venous pressure on the left side had risen to 32.5 cm. and on the right to 13.5 cm., and the heart volume, as shown in Fig. 6a, increased 16 c.c. The mean blood pressure could not be accurately measured because of the irregularity of the heart, but the curve shows that it was somewhat less than before, whereas the minute volume (790 c.c.) had not decreased. A little later the heart became even more irregular, as is shown in the continuation of this curve in Fig. 6b. At the same time the heart continued to dilate until it was 30 c.c. larger than before the diphtheria toxin was given. At the point, marked 13 on the signal magnet curve in Fig. 6b, 4 c.c. of digilanid C were given. The venous pressures started to decline soon after the digilanid was given, and slowly decreased to 10.3 cm. on the left and 9.7 on the right in approximately 35 minutes. At this time the diastolic volume had decreased 28 c.c. In the meantime, the heart became regular, the output of the left ventricle, neglecting the coronary flow, remained at 790 c.c. per minute, and the blood pressure was 127/104.

In the other experiment with diphtheria toxin, we employed a weaker toxin (L = 0.035). At the start the venous pressure was 7.8 on the left and 11.2 cm. on the right; the flow was 600 c.c. per minute, measured in the flow meter; and the blood pressure was 122/110 mm. Hg. Two hundred twenty c.c. of diphtheria toxin were now introduced into the 1000 c.c. of blood in the reservoir. The heart started to dilate, the venous pressures went up to 11.2 on the left and 15.5 cm. of water on the right,

and the flow decreased to 500 c.c. At the same time the heart became very irregular. The heart had dilated about 15 c.c. at this time, and the flow, as measured in the flow meter, had fallen to 500 c.c. The inflow cock was now opened in order to obtain the same flow as at the beginning, and, with the minute flow at 600 c.c., the venous pressure rose to 20 cm. on the left and 21 cm. on the right. There was at this time a total dilatation of about 42 c.c. The mean blood pressure was very difficult to measure accurately because of the irregularity. We calculated that the mean value was approximately 119 mm. Hg. Therefore the left ventricle was doing about the same amount of work as at the beginning of the experiment, and the mean blood pressure determining coronary flow was, also, the same as at the beginning. Four c.c. of digilanid C were introduced into the reservoir, but the heart continued to be irregular, the venous pressures went up even higher than they had been, and the output decreased. The heart continued to dilate. It was evident that digilanid C would not restore the original condition of this heart muscle, and the experiment was soon discontinued. The experiments with diphtheria toxin show very definitely that this poison tends to produce a hypodynamic heart muscle, but the experiment is frequently complicated by cardiac irregularities. The venous pressure always rises at the same time that the ventricles dilate. There is a tendency toward a fall in the cardiac output which can be made good by increasing the inflow. Under these circumstances the heart dilates more and the venous pressures rise even more. If digilanid C is given soon enough, or if the degree of poisoning is not too great, normal conditions will be restored.

We performed a very large number of experiments in which chloroform was used to injure the heart. The chloroform was introduced into the air that was pumped into the lungs of the preparation, but it was found that it was very difficult to gauge the amount of chloroform accurately by this method, and, in many cases, although we were able to produce a hypodynamic heart muscle, it was very frequently impossible to make the conditions reversible with digilanid C because the poisoning had gone too far. The ventricles would begin to fibrillate, and the heart would stop beating.

Fig. 7a shows continued dilatation* of a dog's heart after chloroform was started. The signal marker shows a slight rise at the moment at which the chloroform was introduced. Shortly after this the heart dilated fairly rapidly. At the end of this curve the heart had increased 18 c.c. in diastolic volume after introducing the chloroform. The cardiac output remained the same as previously, namely, 1165 c.c. per minute. The blood pressure, which was this time taken with a mercury manometer, remained constantly at 84 mm. Hg. The venous pressure, which had been 7.5 cm. on the left and 7 cm. on the right, had gone up to 17 cm.

*In the chloroform series the diastolic position of the cardiometer curve is above the systolic; ergo, there is dilatation when the cardiometer tracing rises. In all the other experiments the opposite is the case.

on the left and 13 cm. on the right at the end of this figure. The heart continued to dilate for a period of about two minutes more, at which time the total dilatation of the heart was 35 c.c. and the flow meter measured a flow of 1040 c.c. per minute. The venous pressure had now gone up to 24 cm. on the left and 16.5 on the right; the blood pressure remained constantly at 84 mm. Hg. This is the condition as seen in Fig. 7b. At the end of this figure the signal marker shows where 4 c.c. of digilanid C were given, and Fig. 7c shows that the dilatation of the heart has receded. Calibration of this decrease in diastolic volume

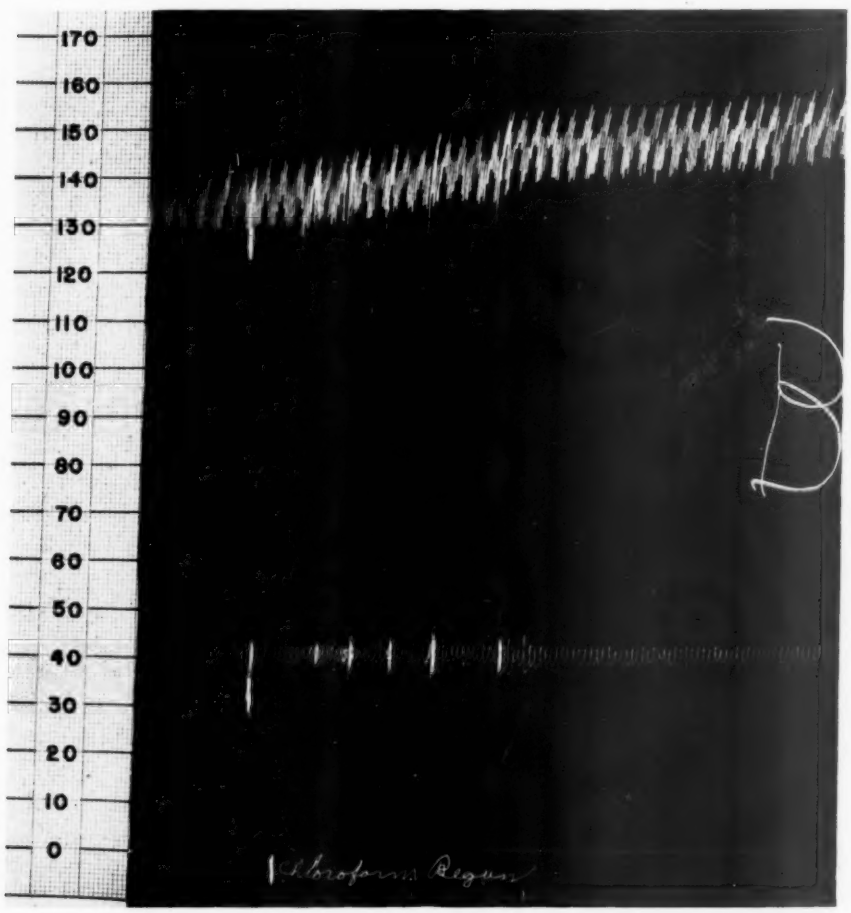


Fig. 7*a*.—Experiment with chloroform. Synchronous points on the cardiometer tracing, the blood pressure tracing, the signal magnet, and the time marker are shown by the three white marks. At the point on the signal magnet shown by the white mark below it, chloroform was introduced. In this curve the cardiometer lever is so placed that an upward deflection indicates diastole, and a downward deflection, systole. In other words, an upward deflection of the curve means dilatation. In this figure the blood pressure tracing is that of a mercury manometer. The zero point for this mercury manometer is the signal magnet line, which corresponds to the point zero on the scale to the left. Chloroform causes 18 c.c. enlargement of the diastolic volume at the end of this cardiometer tracing. The cardiac output remained 1,165 c.c. per minute, exclusive of coronary flow. The blood pressure remained constant. The venous pressure was 7.5 on the left and 7 on the right at the beginning, and, at the end of this figure, had gone up to 17 on the left and 13 on the right.

showed that it amounted to 25 c.c., but the heart was still 10 c.c. larger than at the start of the experiment. The blood pressure remained the same. The minute volume, as measured in the flow meter, had now gone up to 1480 c.c. per minute, which represents a 24 per cent increase over the original output. The venous pressure went down to 13.5 on the left and 11.5 on the right. Undoubtedly, part of the increase in venous pressure and diastolic volume was the result of the fact that the work of the heart had been increased through increased minute volume by about 20-25 per cent. The many experiments with chloroform as the cardiac toxin showed that the heart invariably dilates, the venous pressures rise, and there is a tendency toward a decrease in the stroke output when the

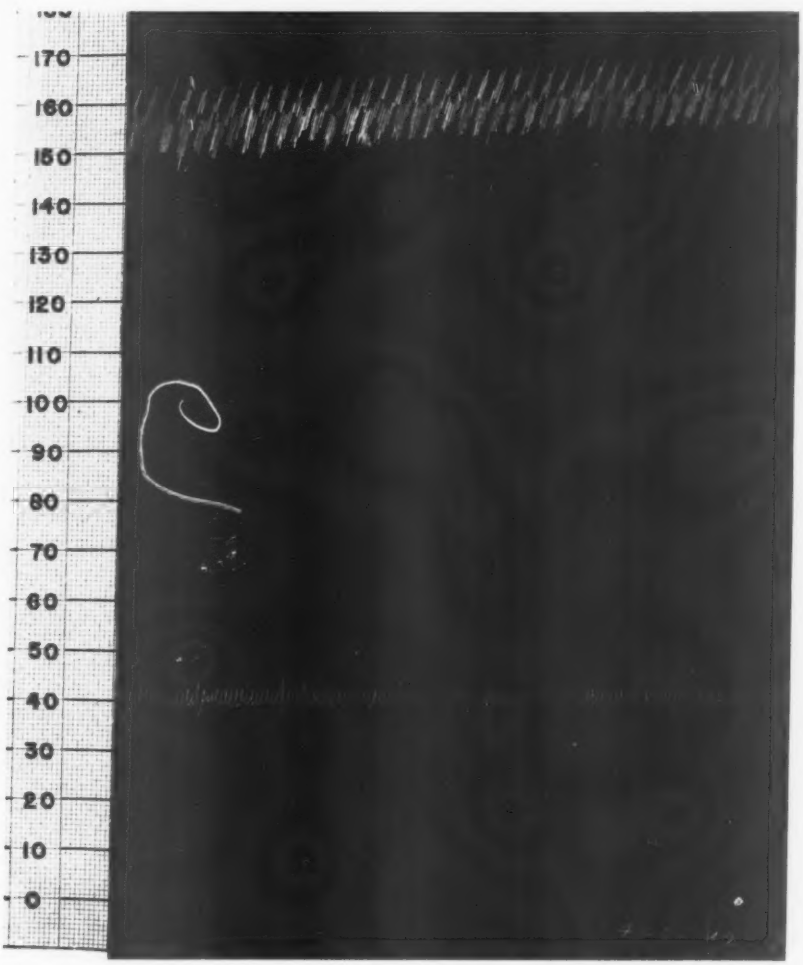


Fig. 7*b*.—This shows continued dilatation of the heart under the influence of chloroform. The total increase in the diastolic volume of this heart near the end of the curve at the point where the digilanid was introduced was 35 c.c., and the flow meter measured an output of 1040 c.c. per minute. Venous pressure on the left had gone up to 24 cm. and up to 16.5 on the right. At the point marked on the signal magnet, 4 c.c. of digilanid C were introduced.

poison begins to affect the heart muscle. If the heart muscle becomes only slightly hypodynamic the original stroke output may be restored. With greater degrees of poisoning the minute output would drop considerably. Frequently a digitalis glycoside (Cedilanid) will restore or nearly restore the original diastolic volume, the original venous pressures, and the original stroke output. If the poisoning has gone too far the glycoside may fail to restore the heart muscle to its original condition, the heart stops beating, and ventricular fibrillation usually ensues.

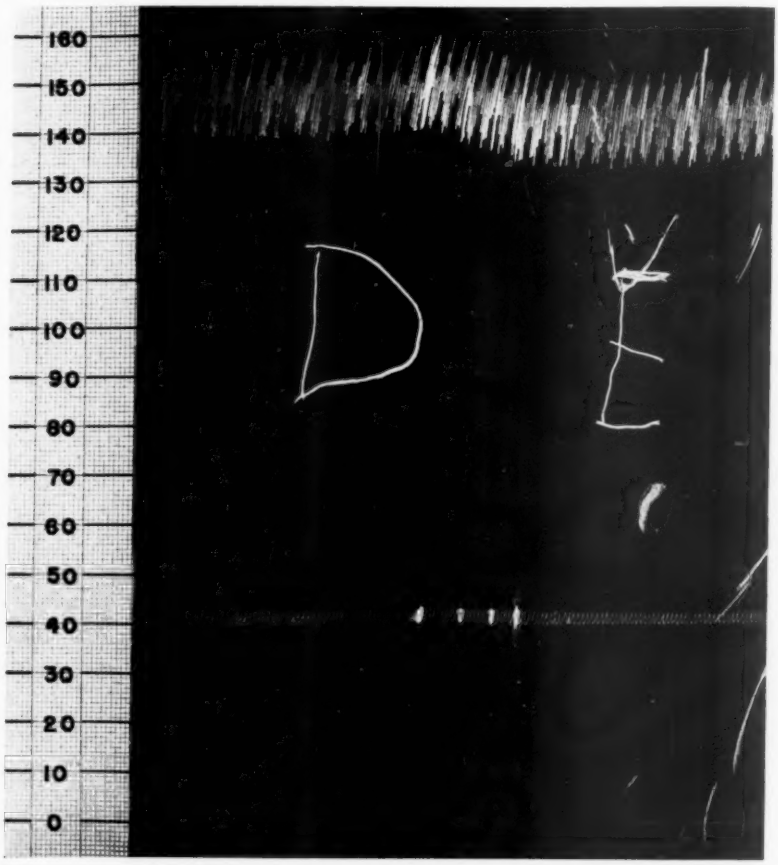


Fig. 7*c*.—Continuation of Fig. 7*b*. The dilatation of the heart slowly recedes, until, at the end of the curve, it has receded 25 c.c. At this time the flow meter measures an output of 1480 c.c. per minute. Venous pressure on the left is now down to 13.5, and, on the right, to 11.5.

The effect of alcohol upon the heart is essentially the same as that of chloroform, chloral hydrate, and diphtheria toxin. Fig. 8a shows an experiment in which 95 per cent alcohol was used. At the start of the experiment the volume flow was 600 c.c. per minute, the blood pressure, 129/97, and the venous pressure on the left 13.2, and on the right 9.6 cm. of water. At the point marked on the signal magnet, 2½ c.c. of 95 per

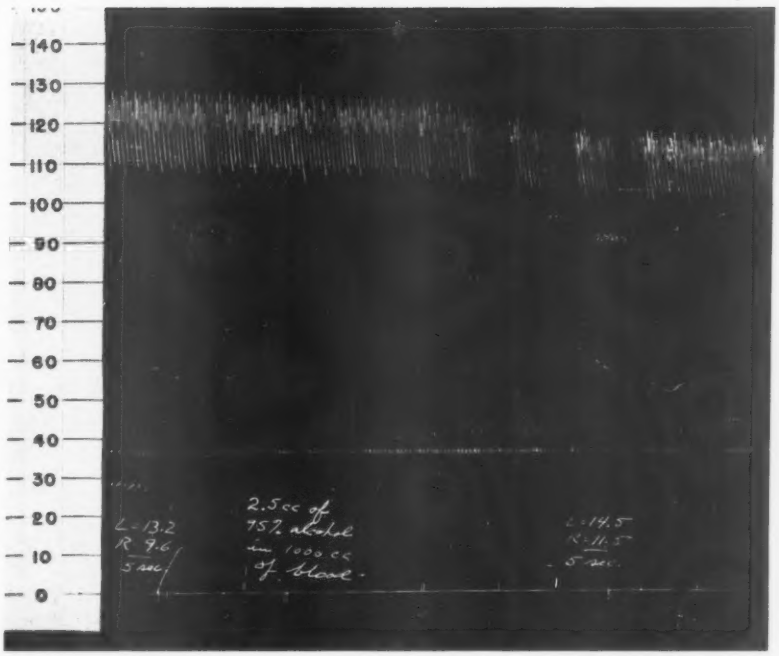


Fig. 8*a*.—This shows the effect of alcohol. At the point marked on the signal magnet, 2.5 c.c. of 95 per cent alcohol were introduced. Dilatation takes place, as seen at the end of the cardiometer tracing. In this case systole is up and diastole down. At the point marked on the signal magnet the flow is 50 c.c. in 5 seconds and the venous pressure on the left has gone up to 14.5 and on the right to 11.5.

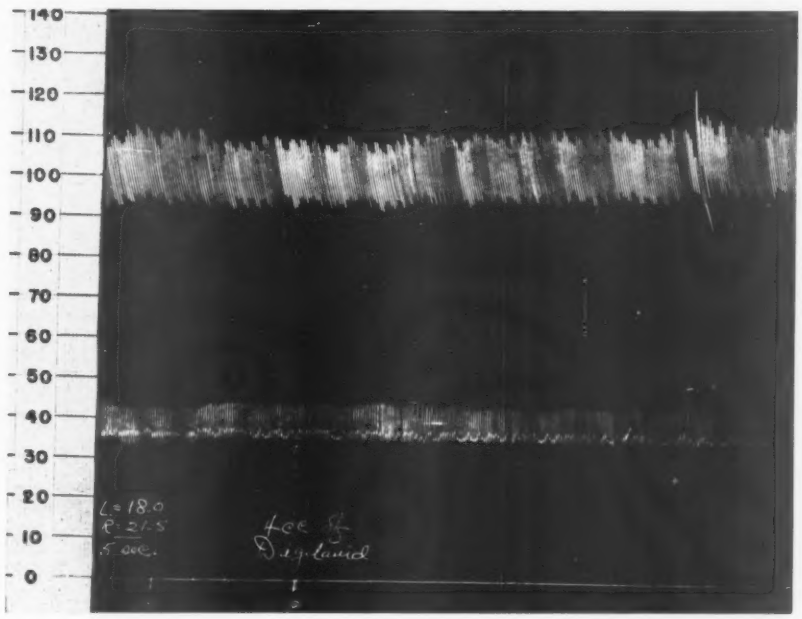


Fig. 8*b*.—Continuation of 8*a*. It shows continued dilatation. The venous pressure has gone up to 18 on the left and 21.5 on the right at the point marked 18 on the signal magnet; at this time the flow is still 50 c.c. in five seconds. Just before the point marked 18 on the signal magnet, the inflow was increased so that the minute flow went up to the original of 600 c.c. At the point "19," four c.c. of digilanid were given and there is some recession in diastolic volume. At the end of the figure this decrease in diastolic volume is about 5 c.c., and the venous pressure on the left is 16, and, on the right, 18.2, with a minute output of 650 c.c., excluding the coronary flow.

cent alcohol were added to the 1000 c.c. of blood in the reservoir. Within one and one-fourth minutes the venous pressure on the left had risen to 14.5, and, on the right, to 11.5, and the diastolic volume of the heart had decreased 7 c.c. The minute output remained unchanged and the blood pressure was 125/95, which was approximately the same as at the start of the experiment. Later, 2½ c.c. more of alcohol were given and the heart dilated again. The venous pressure rose to 16.2 on the left and 13 on the right, and the minute volume fell to 575 c.c. An additional 2½ c.c. of alcohol were given. The heart continued to dilate and the venous pressure to rise until there was a total dilatation of 16 c.c. and the venous pressure was 18.8 on the left and 18.8 on the right. At this time we increased the inflow into the heart because the output seemed to be decreasing considerably. This caused an increased dilatation. Somewhat later we tried the effect of giving digilanid C. At the point marked on the signal magnet, in Fig. 8b, 4 c.c. of digilanid C were added to the blood in the reservoir. At this time the venous pressure on the left was 18, and, on the right, 21.5; the minute output was 600 c.c.; and the blood pressure was 125/97. Three minutes after giving digilanid C the diastolic volume had decreased 5 c.c., as shown near the end of Fig. 8b. Six minutes later the diastolic volume had receded a little more, so that the total decrease in diastolic volume was 7 c.c. and the venous pressure on the left was 16 and on the right 18.2. The minute output had risen to 650 c.c. The blood pressure was approximately 130/96. In this experiment the increased diastolic volume of the ventricles only decreased about 35 per cent under the influence of the digilanid C, partly because we gave too much alcohol or waited too long before giving the glycoside, and partly also because the work of the heart had increased about 10 per cent. This experiment illustrates that when alcohol was used as a poison for the heart muscle, the blood pressure varied very little throughout the experiment, the venous pressure rose very definitely on both sides of the heart, and the heart dilated moderately. At the same time, when the heart failure became severe there was some diminution in the minute output of the heart. A digitalis glycoside (digilanid) tended to decrease the venous pressure and the diastolic volume of the heart and to increase the minute flow.

Only one experiment was performed on the heart-lung preparation without the oxygen consumption apparatus in which potassium chloride was used as the heart poison. Potassium chloride tends to produce heart block and extrasystoles, and these complicate experiments. In this one experiment we made use of a dog weighing 25 pounds. The artificial re-resistance was set at 100 mm. Hg. The inflow was adjusted so that there was a flow of 600 c.c. per minute in the flow meter. The venous pressure was 7.6 on the left and 6.6 on the right. The minute flow, the venous pressures, and the diastolic volume remained constant throughout the preliminary period of four minutes, during which the blood pressure was

127/102. One c.c. of a 10 per cent solution of potassium chloride was added to the 1000 c.c. of blood in the reservoir, and, within two minutes, the venous pressure on the left had risen to 8.5 and on the right to 7.5. The output remained at 600 c.c. a minute. Then another c.c. of the potassium chloride solution was added, and, two and one-half minutes later, the venous pressure on the left was 9.5, and, on the right, 8, with 600 c.c. per minute passing through the flow meter. Three c.c. more of the 10 per cent potassium chloride solution were added, and, four minutes later, the venous pressure on the left had risen to 19 and on the right to 13.2. At this time the cardiac output, minus the flow in the coronary vessels, was 555 c.c. per minute and the heart rate had slowed down very materially. The diastolic volume had increased 10 c.c. The heart became much slower and then very irregular because of numerous extrasystoles. At this time, 5 c.c. of digilanid C were given, but the preparation continued to fail, and, 17 minutes after giving the first portion of digilanid C, the venous pressure on the left was 21, and, on the right, 16; the diastolic volume of the heart had increased 30 c.c. beyond its original volume and the cardiac output, as measured in our flow meter, had fallen to 410 c.c. per minute. At this time the rate of the heart was about 45, whereas it had been 118 before any potassium chloride had been given. The heartbeat was very irregular, and, although the diastolic blood pressure remained fairly constant at 97, the systolic blood pressure varied enormously because of the irregularity of the heart. During the period of greatest dilatation and slowing of the heart, the venous pressures finally rose to approximately 35 cm. both on the left and right. Another c.c. of digilanid was introduced into the reservoir, and, 18 minutes later, the heart had recovered somewhat. The rhythm became perfectly regular, but the rate was 72. The venous pressure fell to 16.5 on the left and 13.5 on the right. The cardiac output rose to 535 c.c. per minute. The blood pressure at this time was 137/97, and the diastolic volume receded until it was only 8 c.c. larger than at the start of the experiment. From this time on there was very little change in the cardiac output, the venous pressures, or the diastolic volume. For a period of 32 minutes after making these measurements they remained constant at the above values. At this time we stopped the experiment because it was apparent that there was not going to be any more improvement in the heart. The effects of the potassium chloride were to cause dilatation of the heart, increase in the venous pressures, decrease in the cardiac output, and slowing and irregularity of the heartbeat. Digilanid seemed to cause disappearance of the irregularity of the heart and a decrease in the cardiac volume and in the venous pressures, but it did not restore them completely to the values present before the potassium chloride had been given. Digilanid also produced an increase in the cardiac output, but here also it did not completely restore it to what it was before the potassium chloride had been given.

## OXYGEN CONSUMPTION EXPERIMENTS

The above-mentioned experiments would make it seem extremely probable that the oxygen consumption of the mammalian heart increases at the same time that the mechanical work of the heart either remains the same or decreases when the heart muscle is made hypodynamic by poisoning. We therefore proceeded to make use of the Visscher oxygen consumption apparatus in order to ascertain simultaneously external cardiac work and oxygen consumption, or total energy release of the heart.

We calculated the work of the left ventricle by multiplying the minute flow in the arterial system by the mean blood pressure. This flow is measured by a Stolnykow stromuhr, inserted in the arterial line. We did not measure the blood flow in the coronary arterial system, so that the work of the left ventricle as thus calculated was probably often 20 to even 30 per cent less than the actual work because of this neglect of the coronary flow. We also assumed that the work of the right side of the heart was one-third that of the left. This is the usual assumption in this type of experimental procedure, especially in view of the increased pulmonary artery resistance caused by the pressure of the cardiometer membrane upon the pulmonary artery. We have neglected the kinetic energy of the mass of blood ejected from the heart, but this is a common procedure in elementary physiology because it is usually assumed that the kinetic energy factor is not more than 5 per cent of the total work of the ventricles. Another thing to be kept in mind is that, although we attempt to measure the work of the ventricles, the work of the auricles is neglected. There is no question that the auricles perform a not inconsiderable amount of work, especially when a cardiometer is placed tightly around the ventricles. Therefore, the work of the heart as we calculated it is undoubtedly considerably less than the actual work, so that our calculated mechanical efficiency is not as high as it would be if it were ascertained by a more accurate method of measurement. At the same time, changes in mechanical efficiency are accurately ascertained by this method. Our mechanical efficiencies are of the same order of magnitude as those observed by Peters and Visscher[6] and Katz and Mendlowitz.[8]

Our first experiment with the oxygen consumption apparatus was carried out with chloral hydrate as the poisoning agent. The dog weighed 19 pounds. The temperature of the water bath in which the heart lung apparatus was immersed was kept at 35° C. The blood pressure was 165/120, giving a mean of 14.2 cm. of mercury. The volume flow was 470 c.c. per minute. The external work of the left ventricle is calculated from these figures as $89 \times 10^6$ ergs. The external work of the right ventricle, calculated as one-third of this, is $29.7 \times 10^6$ ergs. The total work of the ventricles is therefore $118.7 \times 10^6$ ergs. Using the mechanical equivalent of heat, this amount of work is equal to 2.8 calories. The oxygen consumption of the heart-lung preparation was measured over a period of three minutes, and one-third of this was taken

as the number of calories of oxygen consumption per minute. This oxygen consumption was found to be 85 calories per minute. The oxygen consumption of the lung itself is calculated at one-fifth of this, or 17 calories, leaving an oxygen consumption for the heart of 68 calories. The mechanical efficiency, as calculated from these figures of 68 calories oxygen consumption for the heart and 2.8 calories of external ventricular work, was 4.1 per cent.

Now 6 c.c. of a 20 per cent solution of chloral hydrate were put into the reservoir containing the blood. Eleven minutes after the chloral hydrate had been given, the following observations were made. The blood pressure was 168/113, giving a mean of 14 cm. of mercury. The minute output, as measured by the flow meter, was 455 c.c. per minute. The external work of the ventricles was equivalent to 2.7 calories. The oxygen consumption of the heart-lung preparation for one minute was 131 calories, and, of the lung, 17 calories, leaving 114 calories as the oxygen consumption of the heart per minute. The mechanical efficiency under these circumstances was calculated as 2.4 per cent, which was a fall of 41 per cent within eleven minutes after giving the chloral hydrate. The dilatation of the heart at this time, as measured by the cardiometer, was 21 c.c.

Six minutes after 4 c.c. (0.8 mg.) of digilanid were given, the blood pressure was 167/115, giving a mean blood pressure of 14.1 cm. of mercury. The minute output of the heart at this time, as measured by the flow meter, was 526 c.c. The external work of the ventricles for one minute, as calculated in calories from the mean blood pressure and the flow, was 3.2 calories. The oxygen consumption of the whole preparation for one minute was 118 calories. Subtracting 17 calories for the oxygen consumption of the lung for one minute leaves 101 calories for one minute. This gives a mechanical efficiency of 3.2 per cent six minutes after digilanid was given, or an increase in mechanical efficiency of 33 per cent. The diastolic volume now showed approximately no enlargement. Nine minutes after giving the digilanid C the external work of the two ventricles, as measured in calories, was 2.9 calories, and the oxygen consumption of the heart for one minute was 88 calories. This gives a mechanical efficiency of 3.3 per cent, or a 37 per cent increase within nine minutes after digilanid C had been given.

We tested the cardiometer very carefully in this experiment, and found that there were no leaks. This was a good preparation from the start. A check made at the beginning of the experiment showed that for eight minutes of the normal period there was no dilatation of the heart, but rather a 1 c.c. reduction of the diastolic volume. At the same time we measured a reduction in the external work of the left ventricle of about 1 per cent. This shows that this was an exceptionally good experiment, and that spontaneous failure proceeded very slowly. The dilatation and the change in oxygen consumption and mechanical

efficiency after the chloral hydrate was given may therefore be well attributed to the effect of chloral hydrate alone. In the same way it may be said that the effect of the digilanid alone caused the dilatation to recede and the mechanical efficiency to increase after it had been reduced by the chloral hydrate. This experiment proves that chloral hydrate causes a reduction in the mechanical efficiency of the heart muscle at the same time that it produces an increase in the diastolic volume of the heart.

A second experiment was done with chloral hydrate as the poisoning agent, making use of the Visscher oxygen consumption apparatus to ascertain mechanical efficiency. In this experiment it took us a long time to get the preparation made. Therefore, the heart had dilated considerably before it was put into the cardiometer. In this experiment the calculated external work of both ventricles for one minute was $65.2 \times 10^6$ ergs, which is equal to 1.6 calories when the mechanical equivalent of heat is used for the transformation of ergs into calories. The oxygen consumption of the heart for one minute was 172.5 calories, and the mechanical efficiency was therefore 0.92 per cent.

Now 4½ c.c. of a 20 per cent solution of chloral hydrate were put into the venous reservoir. Within a short period of time there was a distinct dilatation of the heart, amounting to about 10 c.c., but, as there was a slight leak in the cardiometer, the dilatation was probably greater than this. The minute output decreased to 142 c.c. per minute, as measured in the flow meter. It was impossible to increase this minute output because the stopcock between the venous reservoir and the right auricle was wide open. The external work of both ventricles per minute was now 0.78 calories. The oxygen consumption of the heart alone for one minute was 191.9 calories. This gave a mechanical efficiency of 0.46 per cent. The mechanical efficiency fell from 0.92 per cent to 0.46 per cent after the use of chloral hydrate, that is, to one-half what it had been previously.

Four c.c. of digilanid C were now put into the reservoir, and the cardiometer tracing showed a distinct reduction in size five minutes afterwards. The external work of both ventricles was calculated as 2.6 calories of ventricular work. The oxygen consumption of the heart was 133.9 calories. This gives a mechanical efficiency of 1.9 per cent after the digitalis glycoside had been given. This experiment shows very definitely that, when the heart muscle was poisoned with chloral hydrate, the mechanical efficiency diminished to one-half its previous value, and the use of digilanid resulted in an increase in the mehanical efficiency of 300 per cent. In this experiment there was a large spontaneous loss of mechanical efficiency before the poison was administered, part of which loss was removed by the use of the digitalis glycoside.

One more experiment was performed with chloral hydrate. This was again a poor preparation because of the long time consumed in making it, in fitting the cardiometer, and getting everything to work accurately.

After the heart-lung preparation had been completed, we had trouble with the apparatus, the valves, and the tubing, so that one and one-half hours elapsed between the time of completing the heart-lung preparation and the time at which it was finally put into the cardiometer. During this period the heart had dilated very greatly, so that it completely filled the cardiometer and therefore could not dilate. The temperature of the water bath was 34° C. Before the chloral hydrate was given, the output of the left ventricle, as measured in the flow meter, was 300 c.c. per minute. The blood pressure was 165/105. The external work of the two ventricles was calculated from these data as 1.6 calories per minute. The oxygen consumption of the heart alone was 384 calories, giving a mechanical efficiency of 0.4 per cent. Now 3 c.c. of a 20 per cent solution of chloral hydrate were introduced into the venous reservoir, but there was no dilatation, which corresponds with the fact that dilatation was almost impossible because the ventricles practically filled the cardiometer. On the other hand, there was a distinct fall in the blood pressure, and the stroke output seemed to be definitely less. An attempt was made to increase the inflow, but this was not successful because the heart could not dilate. After the heart had been under the influence of the chloral hydrate for four minutes, the minute output of the left ventricle had decreased to 90.5 c.c. per minute and the blood pressure was 125/85. The external work of both ventricles was $17 \times 10^6$ ergs, which is equivalent to 0.4 calories. The oxygen consumption of the heart alone for one minute was 374 calories, which gives a mechanical efficiency of 0.1 per cent. Now 4 c.c. of digilanid C were introduced into the reservoir, and, within 10 minutes, the minute volume, as measured in the flow meter, rose to 176 c.c. and the blood pressure was 155/90. The external work of the two ventricles was now equivalent to 0.9 calories. The oxygen consumption of the heart was 364 calories, which gives a mechanical efficiency of 0.25 per cent. It will be noted that this experiment was done at practically constant diastolic volume because the heart filled the cardiometer. In accordance with this, the oxygen consumption remained practically constant throughout the experiment. On the other hand, the external work of the heart decreased greatly. This experiment shows that, under the influence of chloral hydrate, even when the ventricular volume remained constant, there was a decrease in the mechanical efficiency, and the effect of digilanid C was to increase the mechanical efficiency.

Our next experiment on oxygen consumption was performed with alcohol as the heart poison. The heart, taken from a 24-pound dog, seemed to be in excellent condition. Some dilatation took place before the cardiometer was placed over the ventricles, but, after the preparation was started, the heart did not dilate over a period of six minutes. The minute volume also remained constant, as ascertained by four different measurements within a period of four minutes. This minute volume was

405 c.c. per minute. The blood pressure was 205/120, giving a mean of 162. The external work of the two ventricles was 2.8 calories. The heart consumed 225 calories of oxygen per minute, giving a mechanical efficiency of 1.2 per cent. A couple of minutes later a second measurement of the external work of the two ventricles showed that it was 2.7 calories. The oxygen consumption of the heart itself was 249 calories per minute giving a mechanical efficiency of 1.1 per cent. Now 6 c.c. of alcohol were introduced into the venous reservoir. Eleven minutes after the alcohol had been given, the heart had dilated about 6 c.c. and the minute output of the left ventricle had declined slightly (to 395 c.c.). The blood pressure had fallen to 200/115, giving a mean blood pressure of 158. The external work of the two ventricles was 2.6 calories. The oxygen consumption of the heart alone was 268 calories per minute, giving a mechanical efficiency of 0.95 per cent.

Two c.c. more of alcohol were added, and, 13 minutes later, the diastolic volume increased a little more. The minute output had now fallen to 306 c.c., and the blood pressure was 195/115, giving a mean blood pressure of 155. The external work of the two ventricles was 2.0 calories. The oxygen consumption of the heart during this period was 278 calories per minute, giving a mechanical efficiency of 0.7. Therefore, 30 minutes after the first alcohol had been introduced into the system the mechanical efficiency had fallen 36 per cent. There were now 8 c.c. of alcohol in the system, giving approximately an 0.8 per cent solution of alcohol by volume. Another measurement was made 10 minutes previous to the last measurement quoted, and also after 8 c.c. of alcohol had been introduced. At this time the minute output was 333 c.c., the blood pressure, 185/115, and the external work of the two ventricles, 2.0 calories. The oxygen consumption of the heart, as read from the spirometer curve, and after deduction of the amount consumed in the lungs, was 274 calories, giving a calculated mechanical efficiency of 0.7 per cent. Fifteen minutes after the last alcohol had been introduced into the system, 4 c.c. of digilanid C were introduced into the reservoir. Ten minutes after this the blood pressure was 225/115, and the minute output had risen to 575 c.c. The calculated external work of the left ventricle was therefore 4.1 calories. The oxygen consumption of the heart alone was 286 calories, giving a mechanical efficiency of 1.4 per cent. The volume of the ventricles was now 5 c.c. less than at the beginning of the experiment, but we must take into consideration that there was a slight leak in the cardiometer. This experiment shows that alcohol reduces the mechanical efficiency of the heart at the same time that the heart dilates, and that digilanid C makes the mechanical efficiency even better than at the start of the experiment.

The one experiment with diphtheria toxin was not completely satisfactory. We had at our disposal a comparatively weak diphtheria toxin ($L = 0.035$). Moreover, as is frequently the case with diphtheria toxin,

an arrhythmia was produced. The rate became rapid and the beating irregular. The results are never quite as clear-cut when arrhythmias complicate the picture. The heart-lung preparation, which came from a dog weighing 18 pounds, seemed to be in excellent shape. The work of the ventricles before diphtheria toxin was given was 3.1 calories. The oxygen consumption of the heart was 183 calories, giving a mechanical efficiency of 1.7 per cent. One hundred eighty c.c. of the diphtheria toxin were put into the reservoir, and, 41 minutes later the work of the heart in calories was 3.2, and the oxygen consumption of the heart for one minute was 287 calories. This gave a mechanical efficiency of 1.1 per cent, or approximately a 35 per cent diminution in mechanical efficiency. Four c.c. of digilanid C (0.8 mg.) were injected into the reservoir, and, 13 minutes later, the work of the ventricles was 3.3 calories and the oxygen consumption of the heart for one minute was 223 calories, giving a mechanical efficiency of 1.5 per cent. Five minutes later the work of the ventricles and the oxygen consumption were the same. We suspect that auricular fibrillation was present but could not settle the question definitely.

We attempted one experiment with potassium chloride, but we were unable to calculate the work of the ventricles accurately after giving the potassium chloride because the rate became very slow and the beating was very irregular; the cardiac output measurements were very unequal, and we felt that it was impossible to make an accurate estimation of the work of the ventricles because of the impossibility of obtaining accurate mean blood pressure values.

These experiments show that, when the heart muscle is rendered hypodynamic by a poisoning agent, the first effect is to reduce the ratio of external work that can be performed when a given amount of oxygen is consumed in the combustion of energy releasing materials. Consequently, the heart is not able to pump as much blood per beat, if the blood pressure is kept constant, because the amount of external work must decrease. This leads to retention of blood in the ventricles at the end of systole. Blood is flowing from the periphery with the same velocity, for the moment, as before the heart muscle started to fail, and, in consequence, there will be an increased amount of blood within the ventricles and some rise in the intraventricular pressures, as well as in the auricular pressure at the end of diastole. A rise in auricular pressure will lead to increased venous pressure. The rise in intraventricular pressure at the end of diastole leads to increased stretching of the heart muscle fibers and increased diastolic volume. The increased diastolic volume results in an increased oxygen consumption, or an increased consumption of energy releasing materials in the heart muscle. In consequence, there will be an increased amount of energy available for external work after dilatation has been effected. Ultimately there is a tendency toward restoration of the amount of external work performed by the heart muscle, but at the cost of increased oxygen consumption, in-

creased diastolic volume, and increased venous pressure. If the heart muscle becomes only slightly hypodynamic and the blood pressure remains constant, increased diastolic volume will be sufficient to keep up the stroke output at approximately its previous value. But with higher degrees of injury to the heart muscle, the consequent rise in venous pressure is not sufficient to dilate the heart enough so that it can eject the same amount of blood as previously, even with increased oxygen consumption. Under these circumstances the stroke and minute output, as well as the external work of the heart, diminish considerably. By increasing the input of blood, and thereby raising the venous pressures to very high values, we can, in the heart-lung preparation, frequently keep the stroke and minute output constant, despite considerable poisoning of the heart muscle fibers, but at the cost of a very marked increase in oxygen consumption.

The primary effect of digitalis is again demonstrated to be that of an increase in the mechanical efficiency of the heart, as first stated by Peters and Visscher,[6] and when this occurs the heart is able to pump more blood in its dilated state. In consequence, part of the residual blood in the ventricles, as well as in the venous reservoirs, is pumped out, the dilatation recedes, and the venous pressure declines. Digitalis may restore the previous condition, or there may be some increased venous pressure and dilatation after the digitalis effect is complete.

## CONCLUSIONS

The cardinal features of spontaneous heart failure or that produced by chloroform, chloral hydrate, alcohol, and diphtheria toxin are (a) a decrease in the mechanical efficiency of the heart; (b) dilatation of the ventricles; (c) a rise of venous pressure in the left and right auricles; and (d) a tendency toward a decrease in the minute output of the ventricles.

When the heart is poisoned with potassium chloride the ventricles dilate, the venous pressure rises in the left and right auricles, and there is a tendency toward a decrease in the ventricular output.

In one experiment in which the diastolic volume and the oxygen consumption were kept constant, there were a decrease in the mechanical efficiency of the heart, a tendency toward a decrease in the minute output of the ventricles, as well as the mean blood pressure, and a rise of venous pressure in the left and right auricles.

Digilanid C (Cedilanid), a digitalis glycoside, increases the mechanical efficiency of the heart provided the heart failure has not been allowed to go too far. It increases the cardiac output, decreases the ventricular dilatation, and decreases the venous pressures.

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## DISCUSSION

Dr. George Herrmann, Galveston.—These experiments of Drs. Fahr and Buehler are very interesting with respect to the progress of the mechanics of heart failure. In the early work that we reported on the chemistry of heart failure, we did experiments somewhat similar to those which Dr. Fahr has presented, except that we carried the hearts to spontaneous exhaustion and then studied the changes in the chemistry of the heart muscle. It must be remembered that we are dealing in these animal experiments with normal hearts that have a good coronary arterial system. Such relatively young hearts might possibly compensate by increased oxygen consumption, which could not be made available to the heart muscle in the presence of an impaired coronary circulation.

We cannot apply Dr. Fahr's and Dr. Buehler's observations directly to our human problems because it seems to us that in most cases a deficiency in oxygenation of the heart muscle is a primary factor in myocardial insufficiency. Chemical change is an equally large factor, at any rate, and seems to us more important than the mechanical factor.

Diphtheria toxin is a rather unusual cause of failure of the human heart. Of course, the heart which is the seat of valvular disease is under strain, but the chief factor in the hypertensive heart is one of decreased circulation or decreased oxygenation. We have the conception that the trouble begins with the deficiency in oxygenation, and that the efficiency of the heart suffers for that reason.

Ruskin pointed out in these experiments that there is both forward and backward failure. The backward failure is that which Dr. Fahr and Dr. Buehler have demonstrated in the rise of venous pressure. The forward pressure was not measured so extensively. The authors stress again the mechanical factor of increased venous pressure as an index of heart failure, as we conceive it clinically.

There are those, of course, who have a conception of heart failure of the forward type, in which venous pressure does not necessarily rise as it did in the experiments that were quoted.

It would be interesting to have, along with these observations on mechanical changes, data concerning the chemical changes that go on in the heart muscle as the mechanical efficiency decreases. I am sure that there would be an index loss of creatine; that is, digitalis sometimes helps in that way to support or exert its tonic effect on the myocardium.

DR. HAROLD E. B. PARDEE, New York.—I am very glad to hear that Dr. Fahr has started on an investigation of heart failure, because I feel that we very definitely need to have a clinical definition of heart failure that is more adequate than the one now being used. He stated that he is progressing from his experimental work to a clinical application.

It has been very disturbing to see the variable meanings that have been given to the term "heart failure" by different writers. Some apply it only to the most severe types, in which the patient is reduced to the state of being in bed. Others apply it to lesser grades of heart failure, when the patient is not particularly ill, but may have râles at the bases of the lungs posteriorly.

I think the important thing to stress is Dr. Fahr's statement that when the heart begins to fail in its mechanical efficiency, that is the beginning of heart failure. It seems to me that this also marks the beginning of human heart failure. In other mords, when the patient is unable, without producing cardiac symptoms, to undertake any physical effort that he had previously been able to make without such symptoms, this indicates the beginning of his heart failure.

What we need and what I hope Dr. Fahr will produce for us is a useful clinical definition.

A committee of the New York Heart Association some years ago tackled this problem and divided heart failure into four grades, calling them Classes 1, 2, 2A, and 3. These titles were later changed to Classes 1, 2, 3, and 4, respectively. This is a measure of heart failure which has been of some use, but it has for some reason removed the emphasis from the underlying condition of heart failure and has not indicated when one should begin to use this term. I believe it is important to use it at the very beginning, at the first sign of the heart's being overtaxed.

DR. GEORGE FAHR, Minneapolis.—I am very glad that I can throw some light on the points that the two previous speakers brought up. Dr. Herrmann talked about the probable difference in the mechanism in coronary disease, when one starts out with a deficiency of oxygen.

Those who have worked for years with the heart-lung preparation could have said, "You don't need to worry about that." When one decreases the supply of oxygen going to the heart muscle with the heart-lung preparation, one gets exactly the same thing as with poison. As venous pressure goes up and dilatation takes place, oxygen consumption increases.

I can report some work, not my own, which has been largely completed, and which shows that this law holds exactly, no matter how the experiment is done. In these very accurate experiments, one can greatly decrease the amount of oxygen going to the heart. It begins to consume tremendously increased amounts of oxygen as it dilates. The supply of oxygen is greatly diminished in those very fine experiments, done in the physiologic laboratory of Dr. Visscher.

With oxygen deficiency the heart consumes more oxygen. Clinicians think that this is a paradox. It sounds like a paradox, but it has to do with the intimate muscle mechanism that takes place when the heart becomes hypodynamic.

The way we carry out this type of experiment on our patients is as follows: We measure the cardiac output, the blood pressure, the venous pressure, and the diastolic volume, which, of course, varies with oxygen consumption. The cases which we have studied in largest degree, because there are so many in our hospital, are cases of coronary disease. These patients come in with heart failure, dilatation of the heart, usually with decreased stroke and minute output, and high venous pressure. We put them to bed and give them digitalis. The dilatation recedes, the oxygen consumption diminishes, and usually work increases. The arterial pressure remains constant and the venous pressure goes down. What is true of heart failure in coronary disease is also true of other kinds of heart failure, such as rheumatic heart disease with valvular

defects. We have all kinds of heart disease, and it is always the same as in the animal experiments with the poison. The patients come in with dilated hearts. After rest and digitalis the dilatation goes down, work increases, and mechanical efficiency goes up.

We have gone over to our dispensary, where we have people with coronary disease, with mitral disease, with hypertension, and with aortic disease, but all we can find is an enlarged heart. They have no symptoms, no dyspnea. The venous pressure is normal, but the vital capacity frequently is low, which means, of course, that there is some left-sided heart failure. But, we have had some patients who had very little decrease in vital capacity. Whether we are justified in saying that there is no venous pressure rise in the left side, I don't know. We have had some patients with very little dilatation of the heart, which is extremely interesting. After digitalis the same thing occurs in these hearts. The diastolic size of the heart diminishes. There is no effect on the venous pressure because it was normal in the first place. But, the mechanical efficiency, or work divided by the oxygen consumption, increases in these hearts which are not demonstrably failing. These patients are running around. They are not doing their usual work, but they are living at home and are not seriously incapacitated.

Dr. Pardee said that he wanted a definition which a clinician could use. I have used the above as a clinical definition now for two or three years. Of course, one cannot define heart failure by means of percussion and auscultation alone. One has to have certain instruments with which to do it. But the investigating clinician can study heart failure on his patients just as easily and almost as accurately as we can in the laboratory.

We took our nurses and our interns with normal hearts and did the same thing. We measured the diastolic volume, the stroke output, and blood pressure. Their mechanical efficiency under digitalis decreases.

The effect of digitalis on a normal heart is exactly opposite to what it is on a hypodynamic heart.

# HEMIPLEGIA FOLLOWING BRADYCARDIA AND CARDIAC STANDSTILL

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THE cerebral manifestations of bradycardia and cardiac standstill are well known. The symptoms are vertigo, faintness, and loss of consciousness, with convulsive seizures and death, depending on the degree of slowing, the length of the periods of standstill, and the physical state of the cerebral arteries. Stokes[1] reported that transient hemiplegia may be a sequel to cardiac standstill. Cardiac standstill of less than two seconds causes a feeling of faintness; of more than four seconds, syncope; and, with longer periods of standstill, from twenty to forty seconds, convulsive movements occur and the respiration becomes slow and the skin pale. Patients usually do not recover from attacks of cardiac standstill which last longer than one to two minutes. Levine and Matton[2] reported a case of Adams-Stokes syndrome caused by ventricular fibrillation and ventricular asystole of five minutes' duration. This was followed by complete standstill of the ventricles for seventy-nine seconds, and, after the intracardiac injection of adrenalin, rapid ventricular contractions reappeared. The phenomena of syncope are caused by cerebral anemia. There are many causes, such as ordinary fainting attacks, postural hypotension, hypersensitiveness of the carotid sinus, cardiac standstill as a result of A-V dissociation, paroxysmal tachycardia or ventricular fibrillation, and aortic stenosis.

This report concerns two patients who had syncopal attacks associated with (1) bradycardia and (2) cardiac standstill, and subsequently developed hemiplegia. No other identical cases have been found in the literature, but two cases of A-V nodal rhythm and syncopal attacks have been reported.[3, 4]

## CASE REPORTS

CASE 1.—R. P., a 36-year-old housewife, was admitted to Lakeside Hospital July 4, 1934, with a history of palpitation and fainting attacks for one month. On the day of admission she had an attack of syncope, with convulsions. During this attack there was no radial pulse. During the next hour several more attacks occurred.

*Past History.*—The patient had had diphtheria and pneumonia in childhood, and hysterectomy five years previously.

*Physical Examination.*—She was a well-developed and well-nourished white woman, in no discomfort. The heart was normal in size and there were no murmurs. The heart rate was 70 per minute and the rhythm was apparently normal. The peripheral arteries were normal and the blood pressure was 120/80. The edge of the liver was barely palpable. The examination was otherwise negative.

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*Laboratory Data.*—The urine was normal; leucocyte count, 17,450; erythrocyte count, 4,970,000; hemoglobin, 93 per cent; blood Wassermann reaction, negative.

The electrocardiograms showed:

July 4, 1934, A-V nodal rhythm (rate 62).

July 5, 1934, A-V nodal rhythm (rate 51) (Fig. 1).

July 9, 1934, A-V nodal rhythm (rate 75).

Fluoroscopic examination of the aorta and heart revealed no abnormalities.

*Subsequent Course.*—During the following years the patient had occasional spells of vertigo and syncope, and her heart rate remained about 48 per minute. On March 29, 1938, she complained of a feeling of weight in the epigastrium on exercise. Her heart was normal in size and there were no murmurs. The blood pressure was 172/90, and the heart rate was 36 per minute. The electrocardiogram showed A-V nodal rhythm, but was otherwise normal. On May 18, 1938, while eating lunch, she suddenly lost the use of her left side and became stuporous. There were no convulsive seizures. She was readmitted to Lakeside Hospital May 22, 1938.

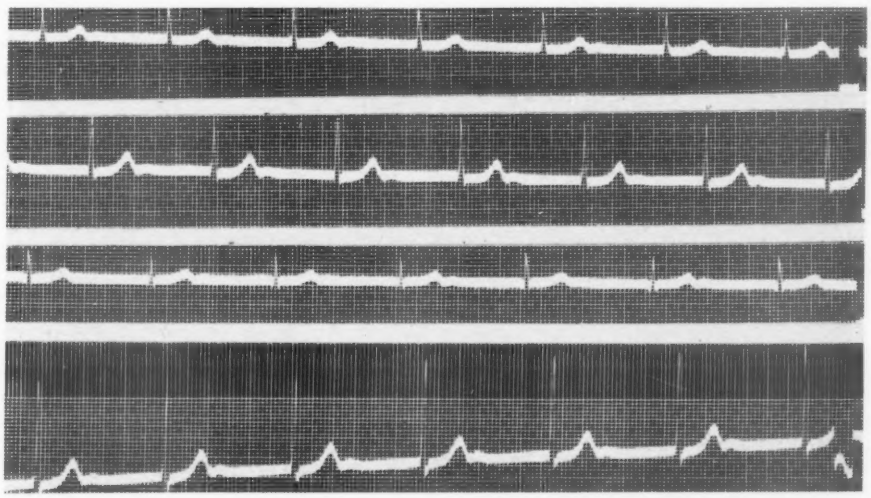

Fig. 1.—A-V nodal rhythm; rate, 51 per minute.

*Physical Examination.*—The patient was in a stupor. The heart was normal in size and there were no murmurs. The rate was 35 per minute and was rhythmic. The blood pressure was 150/90. The left corneal reflex was absent. Both optic discs were normal. The left side of the face was paralyzed, the occipitofrontalis to a lesser degree. The left arm and leg were completely paralyzed. Mayer's reflex was absent in the left hand but present in the right. The left abdominal reflex was absent. Babinski's sign was present on the left. Marked hyperesthesia was present over the left arm. There were no sensory changes over the left leg.

*Laboratory Data.*—Roentgenograms of the skull showed that the sella turcica was normal in size and configuration. There was no evidence of any pathological process in the bones. The electrocardiogram showed A-V nodal rhythm (rate, 35). The spinal fluid was normal in all respects.

The patient has survived, and the cause of the hemiplegia is highly speculative. The patient is young and has no signs of peripheral arteriosclerosis, or arteriolosclerosis, or any other disease that might have caused the condition. During the past three years the paralysis has gradually receded, and now only slight paresis remains. The A-V nodal rhythm has continued, and the rate is stabilized at

approximately 32 per minute. It is suggested that the diphtheria which occurred in childhood was the cause of the disease of the sinus node.

CASE 2.—G. S., a 27-year-old woman, a secretary, was first seen March 17, 1934, complaining of attacks of headache and nausea of thirteen months' duration. A few days previously she had had a fainting attack which lasted one minute. Her pulse rate was 40 per minute.

*Past History.*—She had had diphtheria at the age of 5 years, at which time she was given antitoxin.

*Physical Examination.*—She was a well-developed and well-nourished white woman. The heart was normal in size; there was a soft systolic murmur at the apex. The peripheral arteries were soft, and the blood pressure was 144/80.

Electrocardiogram.—2-1 A-V block; auricular rate, 80, ventricular rate, 40. The record was otherwise normal.

*Subsequent Course.*—On Sept. 11, 1935, she had two attacks of syncope; her blood pressure was 160/80.

Electrocardiogram.—Complete A-V block; auricular rate, 84, ventricular rate, 41. The patient was given ephedrine sulphate in a dose of 0.025 Gm. three times a day.

Jan. 17, 1938.—The patient was admitted to Lakeside Hospital with a complaint of numerous syncopal attacks since the last observation. These attacks occurred without premonitory symptoms, lasted about one minute, and were frequently associated with convulsions, during which she had often fallen and injured herself.

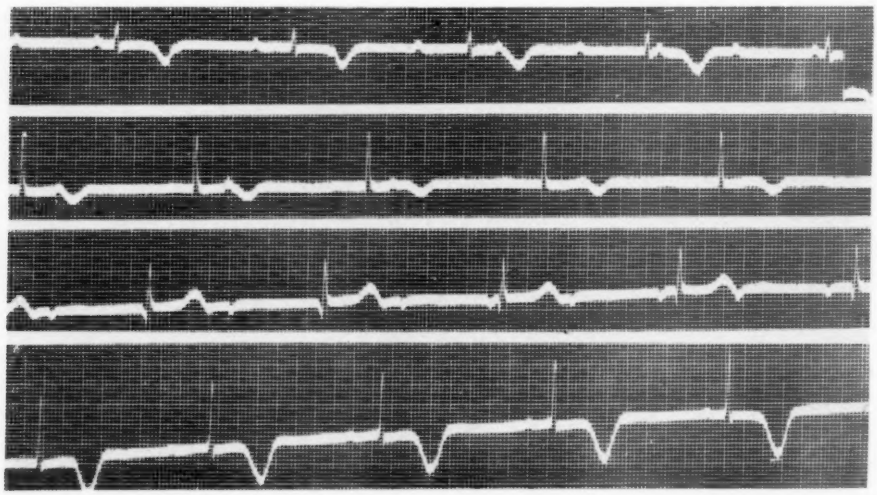

Fig. 2.—Complete heart block. Auricular rate 73; ventricular rate 33. $T_1$, $T_2$, and T in IV R are sharply negative.

*Physical Examination.*—There was nothing significant except the bradycardia (rate, 38) and the blood pressure (105/70).

Electrocardiogram.—Complete A-V block; auricular rate, 73, ventricular rate, 33. $T_1$ was sharply negative and $T_3$ was sharply elevated (Fig. 2).

On the sixth hospital day the patient had a Stokes-Adams attack, lasting one and one-half minutes. On the seventh hospital day another attack occurred, lasting one minute. On the eighth hospital day the patient developed an acute streptococcal throat infection which was successfully treated with sulfanilamide. An attack occurred on this eighth hospital day, and on the ninth day she had a long attack, lasting about thirty minutes, during which the heart rate fell to about

20 per minute and the pulse became almost imperceptible. On the eleventh day another attack occurred, lasting one minute. Adrenalin in a dose of 0.5 c.c. of a 1:1000 solution was given subcutaneously. A few minutes later a second attack occurred, lasting about three minutes, during which no heart sounds could be heard and respirations ceased. Artificial respiration was started and 1.0 c.c. of adrenalin was given by intracardiac injection. One-half minute later the radial pulse could be felt but the heart was rapid and arrhythmic. Later in the afternoon an electrocardiogram showed complete A-V block (auricular rate, 120, ventricular rate, 57). On the next day the complete block was interrupted at intervals by short runs of ventricular tachycardia.

On the fourth day after the long attack of syncope, the patient had an attack lasting four to five seconds, following which she developed a combined (receptive-expressive) aphasia and right-sided hemiplegia and hemianesthesia. Seven days later slight movement returned on the right side, and convalescence progressed. Adrenalin, in a dose of 0.5 c.c. of a 1:1000 solution, was given hypodermically for acute attacks, and ephedrine sulphate was given by mouth (0.025 Gm.) four times daily.

During the following year the patient regained partial use of the right arm and right leg, but there was no recovery of sensation. She continued to have attacks of syncope one to two times a week, and later four to five times a day. Benzedrine sulphate in a dose of 10 mg. was given three times daily, and the attacks occurred less frequently. The attacks again recurred at more frequent intervals and she was readmitted to Lakeside Hospital May 31, 1939, in a semicomatose state; she was having frequent Stokes-Adams attacks. She was given 1 c.c. of a 1:1000 solution of adrenalin, and had but three very brief attacks during the eleven days of hospitalization. She was then given 0.025 Gm. of propadrine hydrochloride three times daily, but continued to have frequent attacks of syncope. She died in an attack on Oct. 30, 1939.

### POST-MORTEM OBSERVATIONS

*Heart.*—The heart weighed 210 grams. The gross appearance was normal. No thrombi were seen in any of the chambers. Histologic examination showed an increase in the amount of connective tissue in the region of the Bundle of His.

*Brain.*—The brain after formalin fixation weighed 1120 grams, and was of firm consistency. There was an area of softening of the left hemisphere in the distribution of the Sylvian artery. This involved the superior and part of the middle temporal convolutions, the inferior frontal cortex at the level of the temporal pole, the lower central cortex, the insular cortex, part of the supramarginal gyrus, and the anterior part of the angular gyrus (Fig. 3). Coronal sections revealed an old, healed area of encephalomalacia composed of yellowish-gray tissue containing an irregular network of connective tissue strands which formed either dense bands or spongy, multilocular, cystlike cavities. The lesion involved the gray and white matter of the third frontal convolution at the level of the genu of the corpus callosum and became more extensive caudally. The inferior portion of the head of the caudate nucleus, the internal capsule between this and the putamen, the external portion of the globus pallidus, and the insular cortex were destroyed (Fig. 4). Further posteriorly, the degeneration lay lateral to the thalamus and involved the white matter and cortex of the parieto-occipital lobe. It terminated at the level of the tip of the posterior horn of the lateral ventricle. The left lateral ventricle was widened. A portion of the anterior superior aspect of the vermis of the cerebellum was softened. Degeneration of the projection tracts had resulted in atrophy of the peduncle and pons on the left and of the pyramid of the medulla on the right.

There was no evidence of vascular disease, vascular anomaly, or embolism or thrombosis of the circle of Willis, of the left middle cerebral artery, or of that portion of the internal carotid artery which was removed with the brain at autopsy.

*Histologic Examination.*—Corresponding areas from the two hemispheres were removed, and the sections stained by the Nissl method. Apart from the area of softening described above, the changes in the cortex were identical on the two sides. The ganglion cells were normal except for scattered, shrunken cells, and

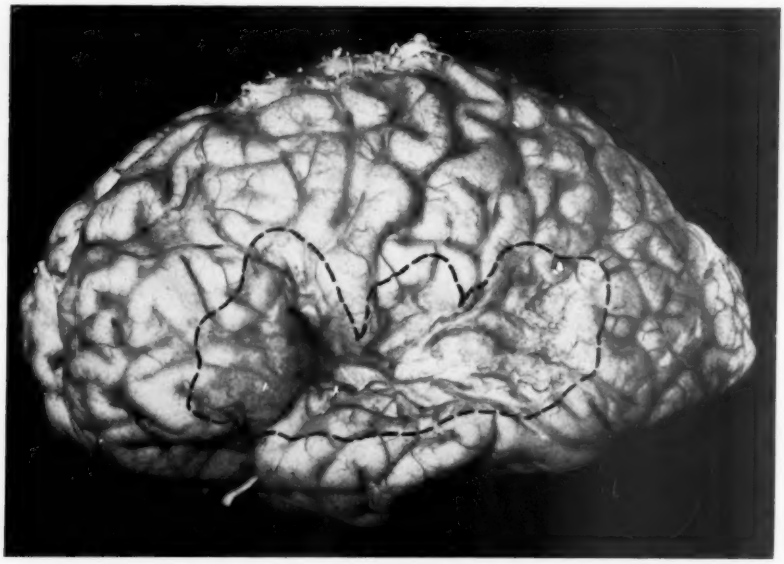

Fig. 3.—Left hemisphere. Broken line shows area of softening visible on the surface.

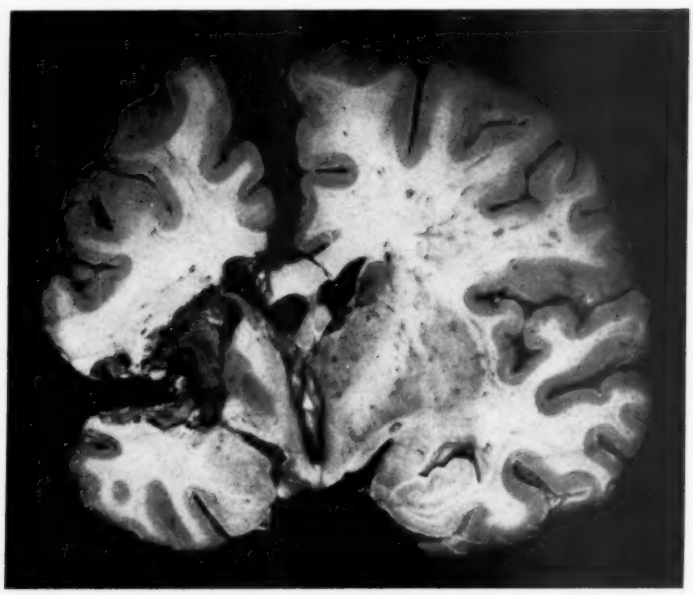

Fig. 4.—Coronal section of brain showing area of encephalomalacia.

there were no diffuse or focal cellular defects. Some of the small cortical arteries were thickened and had hyalinized walls. The type of cell changes in the cortex resembled those which occur in prolonged or chronic illness. In the area of gross softening the parenchymatous elements were replaced by a network of fibrous and glial tissue which contained compound granular cells and debris.

## DISCUSSION

The cause of the encephalomalacia was probably thrombosis of the internal carotid artery in the carotid canal or cavernous sinus. The common carotids pulsated during life but the carotids were not explored at autopsy. Saphir[5] has emphasized the importance of searching for obstruction of the internal carotid artery in the carotid canal and cavernous sinus in cases of encephalomalacia when the obstruction is not found in the middle cerebral artery or in that portion of the internal carotid that is removed with the brain.

The distribution and type of lesion in the brain were similar to those described after obstruction of the middle cerebral artery,[6] carotid ligation,[7] and occlusion of the internal and common carotid arteries.[8, 9]

That the lesion was not caused by a generalized slowing or stoppage of blood flow is confuted by the lack of evidence of anomalies of the circle of Willis and by absence of ischemic changes in the cerebral cortex apart from the area of gross softening.

If there had been generalized ischemic damage to the cerebral cortex in this case it would still be difficult to explain why only that part of the brain supplied by the left middle cerebral artery was severely damaged. Experimental evidence[10, 11, 12] and observations on man[13] indicate that the ganglion cells of the cerebral cortex may be permanently damaged by anoxia for a period of about five minutes. There is evidence[14, 15] that the vulnerability of the neostriatum corresponds to that of the cerebral cortex, but the vital centers in the brain stem have greater resistance. Short nonlethal periods of oxygen deprivation may give rise to syncope, convulsions, or impaired mental function.

The autopsy observations ruled out the possibility that the cerebral softening was caused by embolism arising from a thrombus formed at the site of intracardiac injection, for no injury of the heart wall was found. No thrombi were found in the left ventricle. They also ruled out the possibility of thrombosis in the middle cerebral artery. The strictly focal character of the encephalomalacia and the absence of anomalies of the vessels of the circle of Willis are arguments against the idea that the damage resulted from the generalized cerebral anoxia during the long period of cardiac asystole.

## SUMMARY

Two cases of hemiplegia are reported; one patient had auriculoventricular rhythm, and the other, complete heart block. The latter patient came to autopsy, and widespread encephalomalacia in the area

supplied by the middle cerebral artery was found. No thrombi were found in the arteries. The obstruction may have been in the artery in its course through the carotid canal or the cavernous sinus.

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# Clinical Reports

## BILATERAL MISSED BLOCK

### Report of a Case in Which There Was Left Bundle Branch Block During Life, With Autopsy

I. Mahaim, M.D., Lausanne, Switzerland, M. R. Winston, M.D., Boston, Mass., and H. Roesler, M.D., Philadelphia, Pa.

MICROSCOPIC study in cases of bundle branch block has resulted in contradictory results. Seemingly convincing evidence has been obtained to support both the classical and the new concepts of bundle branch block. One fact seems certain; namely, that the lesions almost always affect both branches of the bundle of His. It is also clear that many of the studies have been based upon an erroneous concept of the normal anatomy of the conduction system. Ever since the work of Tawara and Mönckeberg, it has been assumed that the two branches of the bundle of His remain isolated in their whole course along the interventricular septum, or at least in the first part of this course. But high connections unite the branches and the trunk with the ventricular musculature, and destruction of both branches is compatible with normal auriculoventricular conduction. The association of normal auriculoventricular conduction time with destruction of both branches is a condition that has been described as "bilateral missed block." The case presented here is reported because, in the presence of left bundle branch block (new nomenclature), there was complete destruction of both branches, while high connections united the trunk with the ventricular septal musculature.

#### CASE REPORT

The patient was a 71-year-old man who had shown evidence of left ventricular failure for six or seven years, and of right ventricular failure for six months. Six months earlier he had been examined in another hospital, where the blood pressure was found to be 170/110, and the blood urea nitrogen 35 mg. per 100 c.c. On admission the patient had severe dyspnea, emphysema, and pulmonary congestion. The left ventricle was much enlarged, gallop rhythm and pulsus alternans were present, and the blood pressure was 130/85. The fundi showed nothing of significance. The blood Wassermann reaction was negative, the figures for blood sugar and urea nitrogen were 85 mg. and 18 mg. per 100 c.c., respectively, and the blood cell count was essentially normal. The electrocardiogram showed auricular flutter, with 4:1 block, a ventricular rate of 75 per minute, and occasional premature ventricular beats. The conduction time from the last flutter wave to the initial deflection, as measured in Lead I, was 0.14 second. QRS measured 0.14 second, was of increased voltage,

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and was upright in Lead I and downward in Leads II and III; the S-T segments and the T deflections deviated in opposite directions (left bundle branch block pattern).

*Course.*—Pneumonia developed two days later, and the blood culture revealed a nonhemolytic *Streptococcus viridans*. Another electrocardiogram showed nothing new, except that the flutter was blocked irregularly at times. Renal failure set in, and the patient died five days later. Post-mortem examination revealed pneumonia and empyema, and the smear showed chiefly a nonhemolytic *Streptococcus viridans*. There was an acute fibrinopurulent pericarditis. The heart was much enlarged and weighed 640 Gm. The wall of the left ventricle was 2.0 cm. thick, and that of the right ventricle, 0.8 cm. The valves were normal, the coronary orifices were patent, and the coronary arteries were thin, but did not show any gross evidence of atheromatosis. Microscopic study of the myocardium revealed a very marked increase in the amount of interstitial fibrous connective tissue, especially in the papillary muscles.

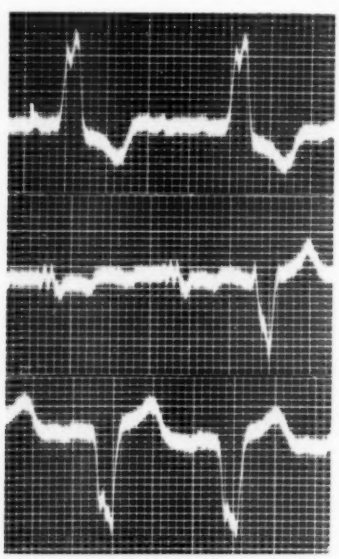

Fig. 1.

MICROSCOPIC EXAMINATION OF THE CONDUCTION SYSTEM

*Method.*—The Tawara node, the bundle of His, and both branches were prepared in two paraffin blocks, and 5,200 serial sections were cut. They were stained by Masson's trichromic method (hemalum-erythrosin-safran). From Block I, color stains were made in one out of fifty sections between numbers 40 and 610, in one out of ten sections between numbers 610 and 1,200, continuously between numbers 1,200 and 1,400, and in one out of ten between numbers 1,400 and 2,750. From Block II, color stains were made throughout in the ratio of one out of each ten sections.

*Results.*—Block I: The Tawara node first appeared on slide 1,060; its artery showed much thickening, but no evidence of syphilis. The atrial myocardium revealed many fibrous patches, but, in spite of this, its communications with the node were well preserved. The common

trunk started at 1,130. Extensive fibrosis of its anterior portion was noted at 1,150, and at 1,200 it appeared to be strangled in the middle, and thus divided into two portions. The anterior portion was much fibrosed. The posterior portion was normal to section 1,228, but was completely destroyed from 1,228 to 1,267, at which point some specific fibers were again observed. These fibers were noted to connect with the ventricular myocardium at 1,281 and 1,299. Fibers of the posterior portion of the trunk were also observed to be in connection with the anterior portion, which had not been completely destroyed at any point, and at 1,341 the fibers of the posterior portion again showed a connection with the ventricular myocardium, which, at this level, however, was entirely fibrosed. The trunk bifurcated at 1,380, and there was complete destruction just below the anterior portion of the left branch. The posterior portion of the left branch could be followed to 1,450, where it also was found to be destroyed. Thus, at 1,450 the whole left branch was entirely interrupted. The right branch at 1,388 was entirely replaced by fibrous tissue. Therefore, at 1,450 both branches were destroyed. At 1,700 some normal fibers were seen in the right branch. At 1,950 half of the right branch was normal; at 2,350, two-thirds; and at 2,620, the whole right branch was normal. Obliteration of the left branch was continuous from 1,450 to the very end of the block.

Block II.—The left branch did not reappear at all. The right branch was easily followed from 2,791, and had a normal appearance to 2,981, showing 40 to 60 cells. From this level to the end of the block there was a constant fibrosis which varied in degree. From 3,191 to 3,231 it was reduced to a quarter of normal; from 3,231 to 3,261, to a third; and thence again to a quarter, to 3,291. A large band of fibrotic tissue cut it apart at 3,501. The branch was nearly normal between 3,551 and 3,561. From here to 4,071 the reduction in size varied between a quarter and one-half of normal, and the number of cells was occasionally reduced to 8 or 10. Starting at 4,381, the diminution was very marked, but a nearly normal appearance was observed rather suddenly at 5,101. In summarizing the observations, it may be stated that the node of Tawara was normal. At its beginning the common trunk was seriously damaged; its posterior portion was connected with the ventricular myocardium at only one place. Just beyond the bifurcation both branches were destroyed and were entirely replaced by fibrous tissue. The left branch was destroyed along its whole course. Destruction of the right branch was noted on 312 slides; it reappeared again further down but showed more or less damage to the end.

## DISCUSSION

The studies of Mahaim,[1, 2] Meesen,[3] and Mahaim and Benatt[4] have demonstrated conclusively that the bundle of His is connected at its very beginning with the musculature of the interventricular septum, and this applies to both the common trunk and its two branches. These high con-

nections, designated as such by Mahaim in 1932, are constant in the human heart, as well as in the heart of the cat, dog, rabbit, pig, and sheep. They are also present in the calf's heart, although Tawara, who studied the bundle of His particularly in this animal because of the marked specific appearance of the bundle there, thought that the branches were completely isolated. Yet it is possible to demonstrate these high connections in the calf's heart also, although it should be admitted that they are much less frequent than in the heart of the cat and the rabbit. Recent studies on this aspect of the comparative anatomy will be published soon by Mahaim and Winston. Obviously, in dealing with the problem of bundle branch block it is important to realize that the common trunk, as well as both branches, is in connection with the ventricular septal myocardium. Any physiopathologic studies with respect to conduction through the diseased bundle of His must include a consideration of these high connections. This is a difficult task. It is customary, in studying the anatomic relations of the branches, to stain only one out of five, ten, or even twenty of the 5,000 to 6,000 sections, according to the nature of the case or the different levels under study. But in order to detect these higher connections, consecutive slides from points where these connections might be expected must be stained and studied without interruption.

When Mahaim examined, in 1932, a case of so-called bundle branch block in which the duration of the QRS complex was extremely long, his findings were surprising and even paradoxical. During life the atrioventricular conduction time had been perfectly normal, but microscopic study revealed complete destruction of both branches in this region. The excitation wave had passed exclusively through the high connections. This condition has been described as "bilateral missed block." Experimental studies along this line were carried out by Rothberger and Mahaim, in 1935, and the microscopic observations made during these studies will be published soon (with Winston). It is interesting that, as early as 1908, Biggs[5] observed lack of constancy in the A-V block which followed destruction of both branches in the rabbit's heart.

Bilateral missed block is not associated with the electrocardiographic features of A-V block, although both branches are destroyed. The duration of the QRS complex is much increased because the excitation wave, in order to reach the papillary muscles and the apical region, follows an atypical path through the musculature of the interventricular septum. The longer the lesions of the small branches along the septum, the larger the QRS area will be. Our patient had auricular flutter with a variable rate of A-V conduction; hence the A-V conduction time could not be ascertained. However, the absence of complete A-V block in the presence of complete interruption of both bundle branches justifies classifying this case as one of "bilateral missed block."

SUMMARY

1. Contrary to common belief, the two branches of the bundle of His are not isolated in their course along the interventricular septum. Connecting branches as high as the top level of the musculature occur in the hearts of men and animals. A continuous series of stained sections must be studied in order to demonstrate these fine connections. In most instances the common trunk of the bundle of His is likewise connected with the ventricular myocardium. Because of the presence of these high connections, the A-V conduction time may be normal in spite of destruction of both branches. This has been designated as "bilateral missed block."

2. A case is reported in which, during life, there were auricular flutter and so-called left bundle branch block (new nomenclature). On microscopic examination both branches were found to be destroyed and the trunk was seriously damaged, but it was possible to demonstrate direct fiber connections with the ventricular myocardium. The excitation wave must have passed these high connection fibers. The absence of complete A-V block in the presence of complete interruption of both bundle branches makes this a case of "bilateral missed block."

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# A CASE OF THROMBOANGIITIS OBLITERANS IN WHICH A STENOSIS VESSEL MURMUR WAS RECORDED THROUGH THE ESOPHAGUS

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THROMBOANGIITIS obliterans was described by Buerger, in 1908, as a chronic disease with inflammatory involvement of the blood vessels. Stenosis or occlusion of the vessel is caused by proliferation of the endothelium or by thrombosis, and disturbed circulation of the blood gives rise to various symptoms.

Formerly it was believed by a number of investigators that the involvement of the vessels was confined to certain peripheral arteries, particularly to the arteries of the extremities, but recently it has been observed that it also occurs in central vessels, such as the aorta and its main branches.

One of the main symptoms of thromboangiitis obliterans is disappearance of the pulsation in the involved artery; it is often accompanied by an ophthalmologic abnormality, such as cataract or abnormal anastomosis of retinal vessels.

Onishi,[1] a Japanese ophthalmologist, reported, in 1907, a case of a vascular disease with loss of vision and disappearance of the radial pulsation. Nakajima[2] reported the same type of case, in 1920; subsequently, similar instances have been observed by various investigators in Japan, including Yoshikawa,[3] Minogoshi and Uchiyama,[4] Tomita and Higashi,[5] Nagashima and Kitamoto,[6] Hayashi and Nishimura,[7] Dodo,[8] and Sato.[9]

In thromboangiitis obliterans, arteriographic examination has been regarded as necessary if one is to ascertain the degree of involvement. When stenosis or occlusion exists in an artery of the extremities or brain, the involved region may be revealed clearly by the arteriogram, but we may not apply this method to central arteries like the aorta or its main branches. Without arteriographic examination, we are obliged to judge the degree of obstruction solely by ordinary physical examination and symptoms.

I have already reported[10] a new method of recording heart sounds through the esophagus, and stated that an aortic murmur may be heard at a distance of 25 to 28 cm. from the front teeth, where the aortic arch is close to the esophagus.

Recently we examined a patient with thromboangiitis obliterans who had no pulsation of the radial arteries on either side. We were not

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able to make an arteriographic examination, but succeeded in recording a loud vessel murmur through the esophagus, which indicated inflammatory involvement of the aorta.

We believe that the recording of a murmur through the esophagus at the top of the aortic arch is one of the important signs of stenosis of one of the great arteries situated close to the heart.

Whether or not a vessel murmur may be recorded through the esophagus in cases of thromboangiitis obliterans or angiitis rheumatica has not been reported. The following is such a case.

## REPORT OF CASE

H. H., a Japanese woman, aged 26 years, was admitted to our clinic Feb. 19, 1940, complaining of visual disturbances and disappearance of the radial pulsation.

*Family History.*—Her grandfather and grandmother died of apoplexy.

*Past History.*—It was stated that she had had no serious illness during her childhood. She married at the age of 23 years. In January, 1939, she consulted a physician who made a diagnosis of spondylitis dorsalis and pregnancy of four months' duration. Therapeutic abortion was recommended, and she had the operation. There was no history of syphilis.

*Present Illness.*—The patient complained of diminution of vision in both eyes, particularly the left, in April, 1938. Ophthalmologic treatment somewhat improved her vision. Thereafter she often complained of dizziness, and sometimes she became faint. In December, 1939, her vision failed again, and she had temporary dysarthria and motor aphasia. She consulted an ophthalmologist, who found a cataract in her left eye. At that time the examiner could not palpate any pulsation in the radial arteries, but the patient stated that she had once palpated it herself.

*Condition on Admission.*—The patient was small, slender, and slightly undernourished. She was pale, but neither cyanosis nor gangrene was present in the extremities. Neither radial pulse was palpable. The carotid pulses were small. No pulse could be felt in either temporal, axillary, or brachial artery. The pulse in the abdominal aorta was normal, but that in the common iliacs, femorals, popliteals, and dorsales pedium was diminished in volume.

The chest was normal. The apex impulse was in the fifth intercostal space at the left nipple line. The right border of cardiac dullness was at the midsternal line, the left border at the left nipple line, and the upper border at the fourth rib. A soft, blowing, systolic murmur was heard over the entire precordium. At the pulmonic area and the base it was slightly louder. At the cardiac apex the third heart sound and a faint systolic murmur were heard. The pulmonic second sound was accentuated.

Examination of the lungs, abdomen, and nervous symptoms revealed nothing of importance.

*Laboratory Examination.*—The erythrocytes numbered 4,930,000, and the leucocytes, 6,400; the hemoglobin was 85 per cent, according to Sahli's method. The urine showed no abnormalities.

Ophthalmologic examination revealed a cataract on the left, anastomosis arteriovenosus retinae coronaria, and diminution of vision in both eyes, particularly the left. The pressure in the central artery was low.

The roentgenogram showed slight, general enlargement of the heart and the aorta. There was no aneurysm of the aorta.

The electrocardiogram revealed right ventricular preponderance and no evidence of myocardial disease.

Microscopic examination of the capillaries in the nail beds of the fingers showed enlargement and marked tortuosity of the arterial and venous vessels on both sides, particularly the left.

The blood pressure was measurable neither by the auscultatory nor palpatory method, because there was no pulsation of the arteries of the upper extremities and no Korotkov sounds could be heard. The blood pressure in the popliteal arteries was 203/150 on the left side, and 190/130 on the right side.

A sphygmogram from the radial artery showed a monocrotic wave with very little amplitude. A sphygmotachogram (by Dr. Tsutsumi, in our clinic) is shown in Fig. 1; it was recorded with extremely high magnification. The blood pressure in the arms and legs was obtained with the help of the sphygmotachogram. In the arms it varied from 40 to 45, systolic, and in the legs it was 132, systolic, on the right side, and 120, systolic, on the left side.

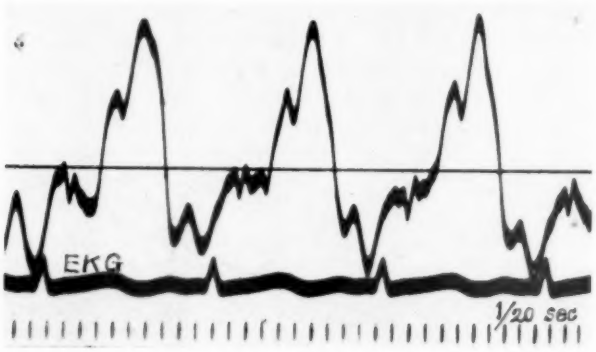


Fig. 1.—Sphygmotachogram from the right radial artery.

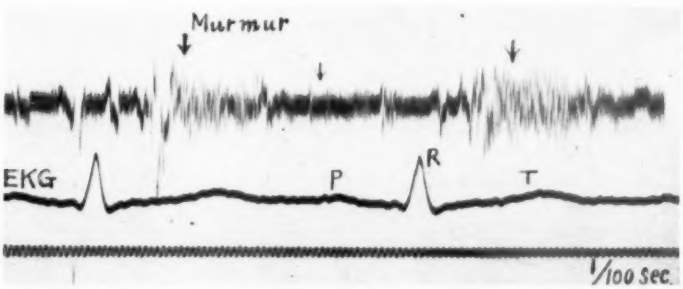


Fig. 2.—Vessel murmur recorded through the esophagus at a distance of 27 cm. from the front teeth. The murmur is present during both systole and diastole.

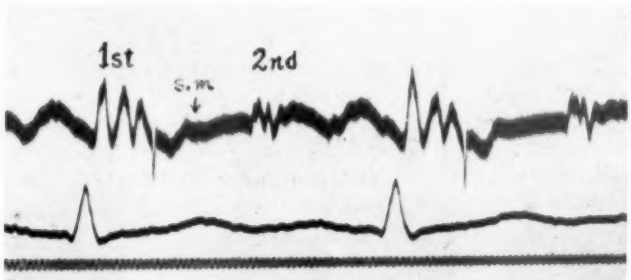


Fig. 3.—The heart sounds recorded through the esophagus at a distance of 37 cm. from the front teeth, to correspond to the left ventricle. Beside the first and the second heart sounds, a systolic murmur is shown as a mere trace.

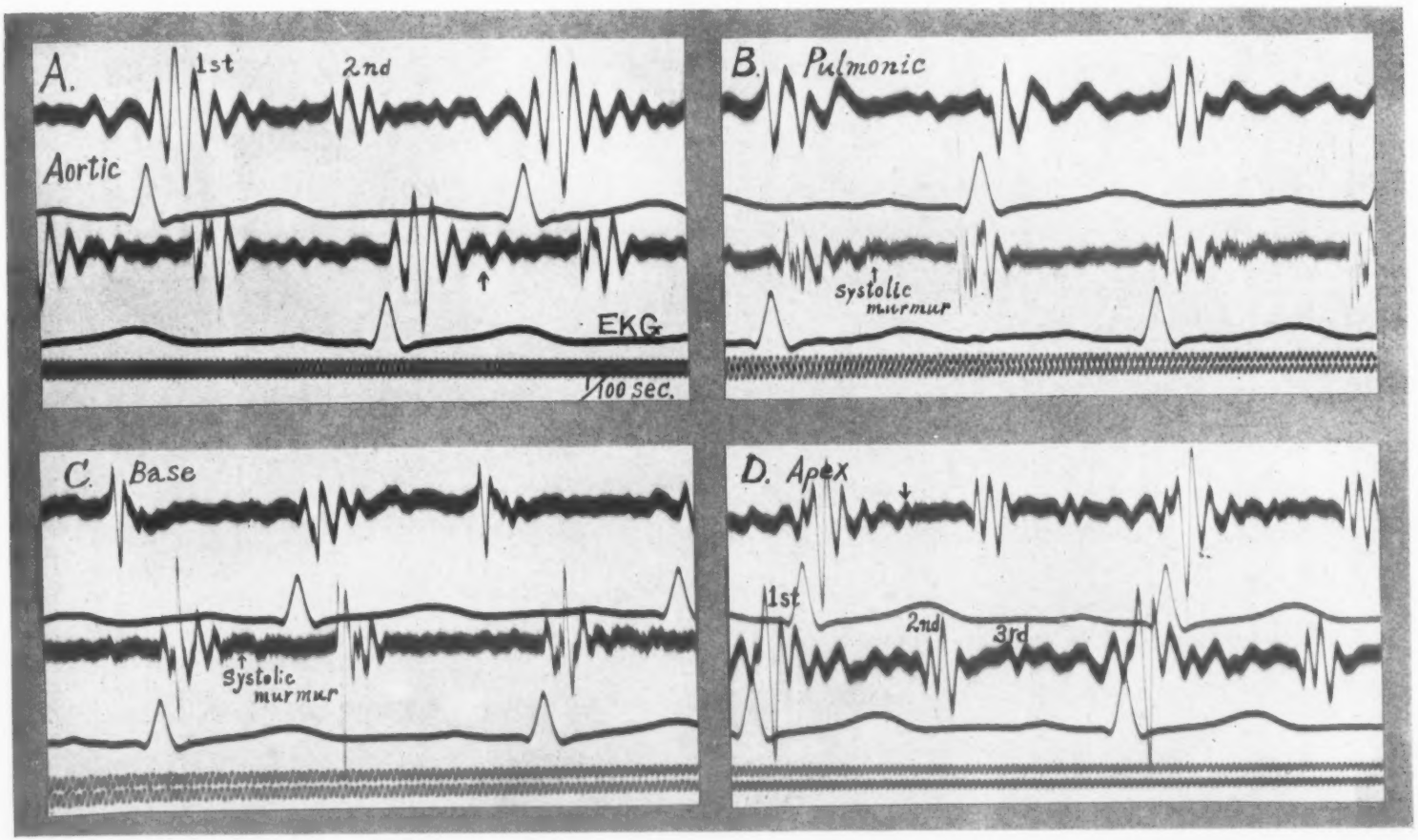


Fig. 4.—The heart sounds recorded over the precordium. (The lower strips in A, B, and C and the upper strip in D were recorded by the use of a high-pass filter. The remaining tracings were recorded without the filter.) Over the aortic area and the apex a systolic murmur is shown as a mere trace. Over the pulmonic area and the base a systolic murmur is fairly well shown. No diastolic murmur is shown in any tracings.

The heart sounds were recorded over the apex, the base, the pulmonic area, the aortic area, and the tricuspid area by means of Koizumi's[11] apparatus. This apparatus utilizes high frequency current. It consists of a microphone, an oscillator, a detector, an amplifier, and an oscillograph. The microphone employed by us was a round metal plate with a diameter of 3 cm.; it was insulated by a mica plate. The microphone was connected to the grid of the oscillator. The chest wall is made to oscillate with each cardiac beat, and the change of electrical capacity between the chest wall, which is earthed, and the fixed metal plate is received and magnified; thus the heart sound is recorded by the oscillograph.

For the recording of a vessel murmur through the esophagus, we employed the method previously reported by the writer.[10] We had the patient swallow an insulated metal cylinder (1.5 cm. × 0.4 cm.), which was connected to the oscillator of Koizumi's apparatus by a fine wire through a rubber tube.

We recorded the sound through the esophagus at a distance of 25 to 28 cm. from the front teeth, and by this means registered a vessel murmur which was far louder than any systolic murmur over the precordium. Fig. 2 shows a vessel murmur from the esophagus at a distance of 27 cm. from the front teeth. It shows a frequency of 120 to 480 per second, and has a large amplitude. The murmur was present during both systole and diastole, and was of maximum intensity during the period of outflow. Fig. 3 is a sound tracing recorded at a distance of 37 cm. from the front teeth. In this tracing a faint systolic murmur is shown, in addition to the first and second heart sounds.

The heart sounds over the precordium are shown in Fig. 4. Over the aortic, tricuspid, and apical areas the systolic murmur was recorded as a mere trace, but over the pulmonic area and the base it was recorded fairly well, with a frequency of 120 to 240 per second. Over the apex the third heart sound was recorded. No diastolic murmur was discovered anywhere over the precordium.

## SUMMARY AND DISCUSSION

Clinical and laboratory examination of this patient led us to the conclusion that she had Buerger's disease, accompanied by ocular symptoms. The cataract on the left side was probably caused by disturbed blood flow in the ocular circulatory system. The dizziness, dysarthria, and aphasia of which the patient complained temporarily were thought to be the result of insufficient cerebral blood flow.

By recording the sounds through the esophagus, we detected a loud vessel murmur with high frequencies. Clinical observation led us to think that this murmur was caused by stenosis near the orifices of the innominate, common carotid, and left subclavian arteries, and that this stenosis had been produced by proliferation of the endothelium, or thrombosis. The circulation in the upper half of the body was disturbed by this stenosis, but an abundance of blood flowed in the lower half of the body via the abdominal aorta, thus causing hypertension in the lower extremities and an increased pulsation in the dorsalis pedis.

The vessel murmur recorded through the esophagus revealed oscillations of high frequencies. Such a murmur may be produced by stenosis of the aortic isthmus, but, in a case of isthmus stenosis, the pulsation of the arteries in the arm is increased, whereas that in the leg becomes smaller.

In our case, a blowing systolic murmur was heard over the precordium, particularly well at the pulmonic area and the base. The roentgenogram and the electrocardiogram revealed no evidence of congenital heart disease or vascular defects. The hemogram showed nothing abnormal. We concluded that this kind of systolic murmur had nothing to do with heart disease or anemia. In the tracing of the sound through the esophagus at the top of the aortic arch, the vessel murmur showed its maximum intensity during the period of outflow of blood from the ventricle. This systolic murmur was, we believe, transmitted to the entire precordium, and particularly well to the pulmonic area.

## CONCLUSION

An interesting case of thromboangiitis obliterans, with inflammatory involvement of the vessels near the aortic arch, is reported. In this case a stenosis vessel murmur was found in the sound tracings which were recorded through the esophagus. For the purpose of locating the region of stenosis in a vessel, arteriographic examination is indispensable, but in a case of angiitis centralis we cannot rely on arteriographic examination. In such a case, we believe, the recording of a vessel murmur through the esophagus aids in diagnosis.

The author wishes to express his thanks to Prof. T. Mashimo, Assist. Prof. M. Maekawa, and Dr. T. Dodo for their helpful criticism and for their assistance in preparing this report.

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# ACUTE, LOCAL, VENTRICULAR ISCHEMIA, OR IMPENDING INFARCTION, CAUSED BY DISSECTING ANEURYSM

## Case Report With Necropsy

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THE clinical and post-mortem earmarks of sudden and permanent occlusion (with myocardial infarction) of one of the main coronary arteries are widely recognized. It is also well known that high-grade, permanent occlusion of one of the main coronary arteries may occur without myocardial infarction. In the latter cases it is presumed that the rate of occlusion is gradual, so that sufficient time is allowed for the development of collaterals. Recently, Wilson and Johnston[1] have again called attention to certain subjective and objective pathologic manifestations in man which they believe are produced by spastic, temporary occlusion of a local division of the coronary arterial tree. They point out the similarity of the electrocardiographic changes in these cases to those which occur experimentally when one of the large coronary arterial branches is temporarily occluded. Inasmuch as these patients always recover, there have been no autopsy observations. The clinical and post-mortem abnormalities produced in man by rapid and high-grade occlusion (without myocardial infarction) of a large coronary branch which is otherwise normal have not, as far as we know, been reported. The case we are presenting is of this variety, and, therefore, is one in which the natural course of events performed an experiment of a rather unusual and fundamental kind. The occlusion was permanent rather than temporary, and therefore myocardial infarction might have been expected to follow. According to our judgment, the heart showed impending infarction. Under these circumstances, the fact that we were able to obtain timely autopsy observations is unique.

### CASE REPORT

The patient, a white, male, pencil salesman, aged 52 years, was brought by ambulance and admitted to the Mercy Hospital-Soniat Memorial, New Orleans, Dec. 28, 1940, complaining chiefly of precordial pain, weakness, and shortness of breath. The onset of symptoms occurred suddenly while the patient was seated in a barber's chair, twenty minutes after lunch. Shortly after the onset he made his way to his doctor's office, where he received a brief examination and an injection of morphine. He was then promptly taken to the hospital. The precordial pain was severe and well localized behind the upper half of the sternum. It did not radiate into any of the extremities and was partially relieved by the morphine. The weakness and sweating were marked, and the dyspnea was moderate. Brief nausea and vomiting occurred. Upon reaching the hospital he complained of a severe aching pain over the right eye.

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Hypertension had been present for at least seven years before the onset of the present illness. About three years before the date of admission he had received a transfusion following a hemorrhage from the bowel. Approximately two years earlier he had been hospitalized for two months because of dull, aching pain in the right hypochondriac region. Slight jaundice was present. A diagnosis of gall bladder disease was made, but no operation was performed and recovery was uneventful. With the exception of occasional palpitation, he had experienced no further symptoms previous to the onset of the present illness. There was nothing in the past history to suggest syphilitic or rheumatic infection.

The admission examination showed a well-developed and well-nourished man, supported by two pillows and displaying slight cyanosis and moderate dyspnea. Throbbing of the carotid arteries and slight engorgement of the neck veins were present. The cardiac apex impulse was forceful and well localized in the fifth intercostal space just inside the left midclavicular line. The rhythm was normal. A loud systolic and a moderately loud diastolic murmur were heard at the aortic area. The former was accompanied by a thrill. Similar murmurs had been heard at his doctor's office shortly before admission. However, in spite of repeated previous examinations, he had never been told that he had heart disease. His admission and subsequent blood pressure readings appear in Table I. The right radial pulse was notably smaller than the left. The lungs were normal, and the remainder of the examination was likewise negative.

TABLE I

BLOOD PRESSURE READINGS IN THE ARMS

| DATE | RIGHT ARM | LEFT ARM |
|---|---|---|
| 12/28/40 | 90/?40 | 140/90 |
| 12/30/40 | 145/100 | 165/98 |
| 1/ 1/41 | 130/90 | 144/98 |
| 1/ 2/41 | 124/72 | 132/78 |
| 1/ 4/41 | 144/90 | 136/82 |
| 1/ 6/41 | 128/78 | 122/72 |
| 1/ 7/41 | 145/90 | 135/82 |
| 1/10/41 | 162/90 | 134/82 |

The red, white, and differential blood cell counts were normal. The blood Wassermann reaction was negative. Urinalysis showed a trace of albumin and many hyaline casts. A roentgenogram of the chest, taken with the patient in bed on the third day after admission, suggested enlargement of the heart and the aortic arch. Serial electrocardiograms, one taken on the afternoon of admission and another on the fifth hospitalization day, are shown in Fig. 1.

Commencing with the second day of hospitalization the patient became comfortable. The cyanosis, dyspnea, sweating, and most of the weakness had vanished. Repeated studies of the blood and urine failed to show any additional abnormalities. The icterus index was 10. The temperature varied daily one degree above and below 101° F. until the eighth day, at which time it gradually became normal. The heart appeared to undergo slow, but progressive, dilatation until the time of sudden death on the fourteenth day. The pulse rate averaged 90 per minute. The patient had just extinguished a cigarette and relaxed on the pillow when he was seen to make a few convulsive movements, after which his respiration ceased. Percussion of the chest after death revealed pronounced precordial dullness of wide extent.

*Ante-Mortem Diagnosis.*—The initial electrocardiogram and the admission blood pressure readings were interpreted by one of us (R. H. B.) to indicate high-grade impairment of blood flow through the right coronary and innominate arteries, respectively. The apparently sudden development of these abnormalities and the aortic insufficiency in a patient who was known to have chronic hypertension led to the im-

mediate diagnosis of dissecting aneurysm. It was further hypothesized that the dissecting column of blood had descended within the aortic wall to the root of the vessel, thus compressing the first segment of the right coronary artery and deforming the aortic valve. The appearance of clinical evidence of either of these events serves to warn of the possibility of fatal hemorrhage into the pericardial sac.[2] The blood pressure readings that were obtained subsequently from the left arm seemed to indicate that the dissection had reached over the arch to the origin of the left subclavian artery. The severe pain over the right eye might have been additional evidence of impaired flow through the innominate artery. The absence of erythrocytes in the urine and of neurologic symptoms in the lower extremities, together with a persistently normal pulsation in the femoral arteries, suggested that the dissection had not entered the abdominal aorta.

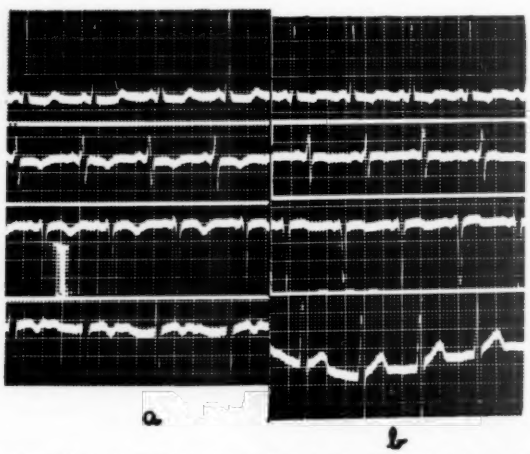


Fig. 1.—*a*, Admission electrocardiogram, Leads I, II, III, and IV F, from above down. *b*, Curve recorded five days after the *a* recording. (See text.)

*Autopsy.*—The pericardial cavity was greatly distended, and, when opened, emitted a gush of 150 c.c. of blood. The remainder of the large pericardial cavity was filled with a huge, red, soft, ante-mortem clot, and with a heart that was apparently of normal size (actually markedly hypertrophied). The free wall of the left ventricle measured 4 cm. in thickness. The valvular measurements were within normal limits. There was a small atheromatous plaque on the base of the posterior aortic cusp which could not have interfered with valve closure. There were two parallel, circumferentially directed, linear tears in the aortic intima; each measured about 1 cm. in length and was located about 5 cm. above the aortic ring on the anterior wall. The aortic media was split by a dissecting column of blood from the aortic ring to the junction of the arch with the descending portion. In the vicinity of the aortic ring the dissection was limited to the right half of the circumference of the vessel, where it partially surrounded the first segment of the right coronary artery (Fig. 2) and communicated posteriorly with the pericardial cavity through a small hole in the adventitia. A fragment of the clot of the dissecting column of blood may be seen (Fig. 2) compressing the arterial segment from above and from both sides. The cross section of the vessel was removed from within the aortic wall; it showed the only discoverable (inoffensive?) atheromatous plaque in the coronary tree. In addition, the dissection extended a few centimeters along the innominate, left carotid, and left subclavian arteries. The dissection of the aortic branches involved only part of the circumference of these vessels, and was of such nature as to transform their

lumina into the shape (on cross section) of the new moon. At the extremity of the arch the dissection again communicated with the aortic lumen through a third intimal rupture.

In spite of the apparent closure of the right coronary artery by the dissecting column of blood, the muscle of the ventricles appeared everywhere normal, except for hypertrophy. The intimal surface of the abdominal aorta presented marked atherosclerosis, which, however, did not extend into the main renal arteries. There was a fusiform, aneurysmal dilatation of the left common iliac artery which measured 4 cm. in diameter. The gall bladder was chronically inflamed and a few gallstones were present.

Fig. 2.—Cross section of the right coronary artery as the latter traversed the walls of the aorta and the dissecting column of blood within the aortic media. The dark area above and on either side of the cross section represents a clotted fragment of the dissecting column of blood. The relationship of this clot to the adjacent tissue structure indicates the compression effect it produced upon the coronary arterial lumen. The white patch at 11 o'clock in the vessel wall is an atheromatous plaque. (See text.)

*Analysis of the Electrocardiogram.*—Inasmuch as the electrocardiographic interpretation was confirmed by the anatomic changes, the manner in which this opinion was reached demands consideration. The opinion was "marked preponderant hypertrophy of the left ventricle, with high-grade impairment of blood flow through the right coronary artery, or impending myocardial infarction."

In 1934, Wilson, Macleod, Barker, and Johnston[3] devised a new method of analyzing the electrocardiogram. Their method consisted of ascertaining the manifest mean electrical axis of QRS and T from the extremity-lead curves by measuring with a planimeter the enlarged areas under the curve of QRS and under the curve of T, respectively. The two axes, thus

obtained, are vector quantities, and, when added (by the parallelogram law), give a new vector which they called the manifest mean electrical axis of QRST, or the ventricular gradient. The three axes are conveniently denoted by $\vec{A}_{QRS}$, $\vec{A}_{T}$, and $\vec{A}_{QRST}$, respectively.* Theoretical considerations and considerable experimental evidence likewise led them to believe that $\vec{A}_{QRS}$ points in the direction in which the accession process travels over the average element of ventricular muscle; that $\vec{A}_{T}$ points in the inverse direction, in which the regression process travels over the average element of ventricular muscle; and that $\vec{A}_{QRST}$ points in the direction of a line along which the local variations in the duration of the excited state are greatest. In less technical terms, the ventricular gradient may be said to point approximately in a direction toward regions of the ventricular muscle in which the average onset of regression is relatively early, and away from regions where the average onset is relatively late. We have seen no further comment upon this important study. Since its appearance, one of us (R. H. B.) has had ample occasion to verify the opinion of the authors that [valuable] information, obtainable in no other way, may be derived by this method of analysis. In order to use the method clinically it became necessary to simplify the technique of measurement.[4] Direct measurements of the electrocardiogram were made by the use of a good hand lens and dividers. Additional error is introduced which reduces the result to an approximation. Nevertheless, as exemplified by the case under discussion, the results have justified the means. In order to make clinical use of the simplified method, it was necessary to obtain some idea of the direction and magnitude of the normal ventricular gradient. A study directed primarily toward this end was undertaken and completed by Bayley, Holoubek, and Baker, in 1940.[4] They were able to confirm Dr. F. N. Wilson's verbal opinion that the normal ventricular gradient has a base-apex direction. Their study showed that it was possible to predict (almost as a rule) the position of the anatomic axis of the ventricular chambers as a result of the collinear relation which normally exists between the anatomic axis (determined roentgenographically) and the ventricular gradient. During the course of their study upon abnormal subjects it was found, among other things, that the T-wave changes which follow myocardial infarction are best described as the result of a clockwise (negative) rotation of $\vec{A}_{QRST}$ with respect to the base-apex axis in "anterior," and a counterclockwise (positive) rotation of $\vec{A}_{QRST}$ with respect to the base-apex axis in "posterior," infarction. In serial curves which displayed maximal T-wave changes caused by infarction, they found that $\vec{A}_{QRST}$ often pointed in the direction of a line drawn from the center of the heart toward the right iliac crest in "anterior," and in the direction of a line drawn from the same point toward the left shoulder in "posterior," infarction. They observed further that these rotations or diversions of the

*The arrowhead simply indicates that the quantity is a vector rather than a scalar.

gradient were invariably accompanied by changes in magnitude. They were able to conclude that diversion of the gradient, after infarction, in so far as it is responsible for most of the T-wave change, may be ascribed (as first pointed out by Wilson and co-workers,[5] and reasserted by Sugarman and associates[6]) to a prolongation of the excited state of the muscle in the immediate neighborhood of the infarcted region. Bayley, Holoubek, and Baker attributed these effects to local ventricular ischemia. A corollary of this assertion is that, after infarction, a reversion of the ventricular gradient following its diversion is caused by disappearance of ischemia from the muscle immediately surrounding the infarct, and is, of course, accompanied by the return of the T waves to a more normal form. Presumably, the disappearance of the local ischemia is the result of establishment in this region of an adequate collateral circulation. For the purpose of the analysis of the electrocardiogram herein presented, the argument may be extended in the following manner.

Let us consider Fig. 3*a*. The solid zone represents dead, the stippled zone, ischemic, and the clear zone, normal, ventricular muscle. Before infarction, but accompanying coronary occlusion, this same region of the ventricular muscle may be depicted as shown in Fig. 3*b*. Here, intense ischemia replaces the dead region. It is possible, therefore, that the same kind of T-wave changes which occur after infarction might also occur shortly before. Theoretically, any differences in the typically abnormal form of T which occur immediately before infarction, and become apparent soon (three weeks or more) after it, should be differences in magnitude rather than kind. This statement neglects the effect on the T wave (usually slight) of the QRS changes, which, in turn, result from the absence during systole of forces previously present in the dead region. One of us (R. H. B.) has observed typical "coronary" T waves heralding infarction on more than one occasion when studying serial curves recorded from patients throughout the development of myocardial infarction.

Approximation of the areas under the curve of QRS and under the curve of T in the admission electrocardiogram (Fig. 1) shows that the $\hat{A}_{QRS}$ (Fig. 3*c*) has undergone an abnormal positive rotation through a polar angle of 70° from the base-apex axis $\hat{H}$ of the ventricular muscle; that the magnitude of $\hat{A}_{QRS}$ is approximately 74.5 millivolt seconds; that $\hat{A}_T$ has undergone a like rotation through a polar angle of 124° from $\hat{H}$; that the magnitude of $\hat{A}_T$ is approximately 21 millivolt seconds; and that $\hat{A}_{QRST}$, having undergone a considerable growth in magnitude, points in the direction of a line drawn from the center of the heart toward the left shoulder. The QRS changes (indicated by $\hat{A}_{QRS}$) are interpreted as meaning marked preponderant hypertrophy of the left ventricle. The development of this variety of QRS change is often accompanied by a gradual negative (clockwise) rotation and growth of $\hat{A}_{QRST}$ which in-

dicate, we believe, a concurrent development of chronic ischemia of the free wall of the left ventricle. The electrocardiograms which typify these last-mentioned axial changes are currently regarded as representing "relative coronary insufficiency."[7] When the negative rotation of $\hat{A}_{QRST}$ that indicates chronic ischemia of the free wall of the left ventricle is compared with its actual position (Fig. 3*c*), as derived for the curve under discussion, it is seen that the direction of the latter is simply the inverse of that of the former. This rather unusual occurrence was the result, we believe, of the presence on admission of high-grade ischemia of the

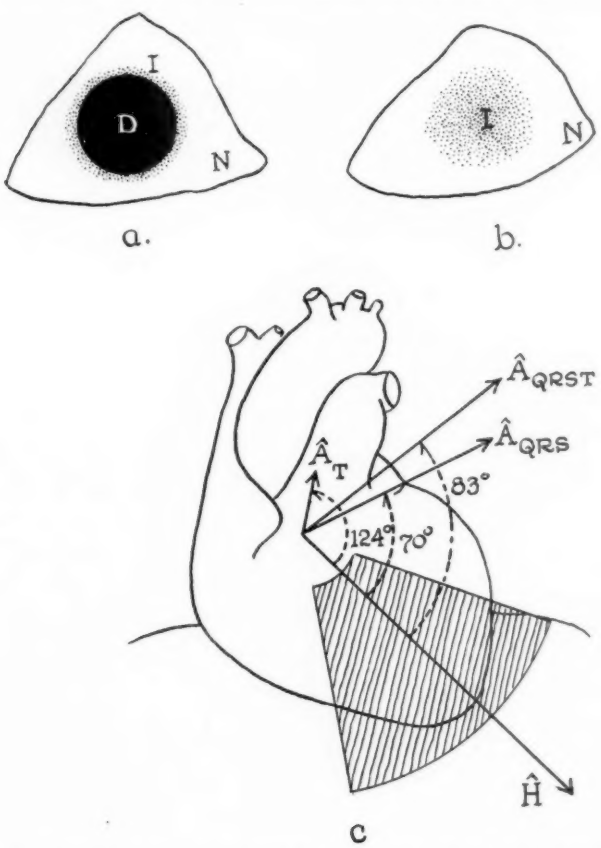


Fig. 3.—*a*, A diagram of region of ventricular muscle, showing an infarct. *D* indicates dead; *I*, ischemic; and *N*, normal muscle. *b*, A diagram of the same region of muscle in the proposed state of impending infarction. *c*, The electrocardiographic axes, $\hat{A}_{QRS}$, $\hat{A}_T$, $\hat{A}_{QRST}$, and the anatomic axis $\hat{H}$ of ventricular chambers. The shaded zone represents the approximate normal region for $\hat{A}_{QRS}$ when $\hat{A}_{QRST}$ and $\hat{H}$ are collinear or in their normal relationship. (See text.)

basal, posterior portion of the interventricular septum and the neighboring diaphragmatic free wall of the left ventricle. In brief, the muscle involved is that ordinarily supplied by the right coronary artery. Moreover, the history of our patient's present illness strongly suggested that the local ischemia was acute rather than chronic. Ante-mortem proof

of the acute character of the ischemia could have been obtained only by a comparison of the curve under consideration with serial curves antedating hospitalization. Unfortunately, no such curves were available.

The second electrocardiogram (Fig. 1), recorded on the fifth day after admission, was analyzed by the same method. The additional T-wave changes in the extremity leads are apparent on inspection. They were the result of partial reversion of $\bar{A}_{QRST}$, and were interpreted as representing diminution in the intensity and extent of the acute local ischemia. The changes in $T_4$ appear to be confirmatory. Curiously enough, a gradual rise in the blood pressure in the right arm took place concurrently. Both of these local improvements may have been related to some single mechanical factor involving the pressure of the dissecting column of blood. In any event, we believe that lessening of the acute ischemia probably played a major role in delaying the development of a "posterior" myocardial infarct.

*The Effects on the Muscle of Acute Local Ventricular Ischemia.*—A number of blocks of muscle were removed from various parts of the wall of the left ventricle for the purpose of microscopic study. Routine tissue stains, as well as stains for fat, showed no differences from one region to another. All of the myocardial changes could be ascribed to hypertrophy. The objective effects of acute local myocardial ischemia in man are, as experimental studies suggest, detectable only by the electrocardiogram.

The electrocardiograms herein presented display T-wave changes (caused by gradient rotation) which are etiologically related to those in tracings demonstrated recently by Wilson and Johnston.[1] Their curves were recorded from five patients with angina pectoris, and differ fundamentally from ours by displaying QRS and RS-T junction changes. Additional changes of this kind are related to acute local ventricular ischemia, but are not, strictly speaking, part of it. On this point, we believe, we are in complete agreement with them. They called attention to the independent variation in magnitude and duration of acute local ischemia, on the one hand, and pain (or subjective changes), on the other. We believe that there is a similar and striking correlation in our case. The pain our patient experienced was typical of that which ordinarily occurs with the onset of dissecting aneurysm. As pointed out elsewhere,[2] it appears to be related to rapid dissection of the aortic wall. Moreover, the pain in our case had vanished by the second day after onset, whereas local ventricular ischemia existed for five days at least (electrocardiographic evidence) or for fourteen days (autopsy evidence). Wilson and Johnston believed that the pain in their cases was of arterial origin (spasm). In our case there was presumably no coronary spasm, but rather a local mechanical compression. We are, therefore, inclined to believe that our patient experienced no pain of cardiac origin. Aside from the evidence which this case adds to theirs, the T-wave changes that

occur immediately before, and persist for a variable, but often long, time after, myocardial infarction are ample evidence that local ventricular ischemia cannot be safely regarded as evidence of the occurrence of cardiac or coronary pain. However, recent opinion has re-emphasized the contrary.[8]

## SUMMARY AND CONCLUSIONS

1. A case is presented in which a dissecting aneurysm led immediately to the production of acute local myocardial ischemia by direct compression of the first segment of the right coronary artery. The aneurysm, the local myocardial ischemia, and the nature of its production were diagnosed before death. The autopsy observations are discussed.

2. The diagnosis depended, to a considerable extent, upon the electrocardiographic interpretation. The latter was reached by a method of analysis described in 1934 by Wilson and co-workers[3]; this method has received little or no comment in the literature, but is one which, on simplification and extension, we believe to be of great clinical usefulness. Using the simplified method, the electrocardiograms herein presented are analyzed.

3. As anticipated, acute local ventricular ischemia of sufficient intensity to produce striking T-wave changes of a kind similar to those that occur in connection with myocardial infarction and last for days or even weeks may be accompanied by no structural changes in the myocardium, and is, more often than not, unassociated directly with cardiac or coronary pain.

We wish to thank Dr. C. F. Bellone for permission to report the case, and Dr. J. R. Schenken and Dr. G. H. Hauser for their kind cooperation in the preparation of the autopsy material.

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3. Wilson, F. N., Macleod, A. G., Barker, P. S., and Johnston, F. D.: The Determination and the Significance of the Areas of the Ventricular Deflections of the Electrocardiogram, AM. HEART J. **10**: 46, 1934.
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6. Sugarman, H., Katz, L. N., Sanders, A., Jochim, K.: Observations on the Genesis of Electrical Currents Established by Injury to the Heart, Am. J. Physiol. **130**: 130, 1940.
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# Abstracts and Reviews

## Selected Abstracts

**Harris, A. Sidney, and Moe, Gordon K.: Idioventricular Rhythms and Fibrillation Induced at the Anode or the Cathode by Direct Currents of Long Duration.** Am. J. Physiol. 136: 318, 1942.*

A method for applying currents controlled as to polarity and rate of flow to the mammalian ventricle is described. Responses from practically the whole ventricular surface were sampled by recording from three local areas simultaneously and changing the positions of the riding contiguous electrode leads from time to time.

Currents, subthreshold for extrasystoles, could give rise to several kinds of changes in the record: 1, "on" and "off" shifts of the base line upon closing and opening the circuit respectively; 2, inflections and changes of level associated with the phases of muscular activity. The amount of displacement of the baseline was reduced during systole, restored to maximal during diastole. After ruling out contact artifacts these features were attributed to conductivity changes associated with contraction and relaxation.

Both anodal and cathodal polarization give rise to oscillating potentials not associated with the phases of the cardiac cycle. The periods of the oscillations were near 40 and 80 msec. Cathodally produced oscillations are higher and are likely to be of the higher frequency (25 cycles per sec., 40 msec. period).

The idioventricular beat threshold was lower for cathodal polarization than for anodal, but the anodal threshold for fibrillation is the lower. The anode is preëminently effective in producing fibrillation. With equal applications of currents near fibrillation threshold 96 per cent of all fibrillations were of anodal origin.

Cathodal polarization of suitable intensity usually produces a tacycardia of regularly spaced idioventricular beats, while anodal polarization produces characteristically irregular rhythms. The point of origin of of the discharges appears to be more constant in anodal polarization. In all cases of fibrillation resulting from polarizing currents induction is via an accelerating series of discharges from the region of the polarizing electrode.

In the discussion, findings from studies on excitation and spontaneous rhythmicity in nerve and muscle are considered and correlated with the observations on fibrillation. Absence of, or a low rate of accommodation appears to be the condition essential to spontaneous rhythmicity and multiple discharges in response to a single excitation. The probable association of the reduction of accommodation by anodal polarization with the great effectiveness of the anode in the production of fibrillation is pointed out. Direct anodal effects of locally reducing the conduction rate and reducing the refractory period are considered and assigned a contributing role.

AUTHORS.

**Graybiel, A.: Diseases of the Heart: A Review of Significant Contributions Made During 1941.** Arch. Int. Med. 70: 303, 1942.

An annual review and discussion of the literature on cardiology. There is an important section on the heart in wartime with special reference to neurocirculatory asthenia.

McCULLOCH.

*See Corrigendum, p. 283.

**Fedorov, N. A., and Shur, E. I.: The Role of the Viscera in Regulating the Temperature of the Body of an Animal Under Physiologic and Pathologic Conditions.** Am. J. Physiol. **137**: 30, 1942.

Thermogenesis in the viscera (liver and intestines) was studied in normal, artificially cooled and heated animals, as well as during febrile states caused by homogeneous and heterogeneous blood transfusions.

The experiments were made on angiostomized dogs with cannulas in the portal and hepatic veins; in each animal the rectal temperature and the temperature of the blood in the abdominal aorta and the portal and hepatic veins were measured.

The thermoelectric method used throughout the experiments detected changes in temperature with sufficient accuracy and made it possible to study thermotopography in the organism.

In normal fasting dogs the lowest temperature of the blood was found in the aorta and the highest in the hepatic vein.

The experiments have shown important thermogenesis in the intestines.

When the animals were cooled by the application of ice to the skin, the difference in temperature between the blood in the hepatic and the portal veins increased, i.e., there was a rise in hepatic heat production (three to six times the original level), providing the blood flow was accelerated; when the animal was overheated, the reverse took place.

Homogeneous blood transfusion did not bring about noticeable changes in thermogenesis in the liver and the intestines, despite a systemic rise in temperature.

The febrile state caused by heterogeneous transfusion is accompanied by a noticeable increase in thermogenesis in the liver and intestines. A comparative study of the hemodynamic variations has shown that the increase in hepatic and intestinal thermogenesis cannot be explained by the influence of circulatory factors.

After anaphylactic shock, the same changes were observed as in the case of heterogeneous transfusion, but the variations in temperature were much greater, especially with respect to the intestines.

The increase in visceral thermogenesis proceeds parallel to the systemic temperature reaction, i.e., the liver and the intestines participate in determining the febrile process accompanying the transfusion of foreign blood.

The use of the method of E. I. London for studying visceral thermogenesis in angiostomized dogs considerably widens the sphere of its application and promises to give results of great practical and theoretic interest.

AUTHORS.

**Hsu, S-H, Hwang, K., and Chu, H-N.: A Study of the Cardiovascular Changes Induced by Stimulation of the Motor Cortex in Dogs.** Am. J. Physiol. **137**: 468, 1942.

By stimulation of the motor focal points on the sigmoid gyrus of the dog anesthetized with chloralose, there is always a fall of blood pressure. The depressor effect thus produced is always associated with the muscular movement in noncurarized animals, but the production of the former is not dependent on the latter.

The intensity of the depressor effect evoked from the cortical stimulation in dogs is determined by the strength of the stimulating current and by the particular motor focal point that is stimulated.

The heart rate is usually increased about 20 per cent on stimulation of the motor area in dogs, but the change of the heart rate is not a casual factor in the depressor effect, since the latter is not influenced or abolished by section of both vagi.

The respiratory movements are usually decreased in amplitude and increased in number, and occasionally apnea may occur during cortical stimulation.

The renal volume is always increased accompanying the fall of blood pressure following cortical stimulation. Vasodilation of the visceral organs is probably the cause of the depressor effect.

AUTHORS.

**Master, A. M., Striker, J., Grishman, A., and Dack, S.: Effect of Undernutrition on Cardiac Output and Cardiac Work in Overweight Subjects.** Arch. Int. Med. **69**: 1010, 1942.

The effect of reduction in weight on the oxygen consumption, pulse rate, blood pressure, cardiac output and cardiac work was studied in five normal overweight subjects who were placed on a 1,200 calorie diet. The modified Grollman acetylene method and the Wetzler-Boeger physical method were used to determine the cardiac output. Loss of weight was accompanied by an average drop of 16 per cent in oxygen consumption, an average increase of 24 per cent in the arteriovenous oxygen difference, and an average drop of 30 per cent in the cardiac output. These changes were accompanied by slowing of the pulse rate and slight lowering of the blood pressure. Since cardiac work is a function of cardiac output and mean arterial pressure, it was calculated that the low caloric intake and the reduction in weight resulted in a distinct diminution in the work of the heart (average, 35 per cent). This is of great benefit to overweight persons, in whom the cardiac work is increased, and is of particular importance in the treatment of patients with heart disease, whose cardiac reserve is diminished and who are barely able to compensate for any additional strain. AUTHORS.

**Sigler, L. H.: The Hyperactive Cardioinhibitory Carotid-Sinus Reflex as an Aid in the Diagnosis of Coronary Disease: Its Value Compared With That of the Electrocardiogram.** New England J. M. **226**: 46, 1942.

A comparative study is presented of the incidence of a hyperactive cardioinhibitory carotid-sinus reflex and of electrocardiographic abnormalities in a series of 1073 cases, largely ambulatory, of coronary disease. It was found that 91.3 per cent of the men and 72.6 per cent of the women in this series showed the cardioinhibitory response, whereas only 63 per cent of the men and 71.9 per cent of the women showed abnormalities in the electrocardiogram. High degrees of cardioinhibitory response, which are definitely abnormal, occurred in 61.8 per cent of the males and 42.9 per cent of the females. Marked electrocardiographic abnormalities occurred in only 37.4 per cent of the males and in 40 per cent of the females.

It is believed that the hyperactive cardioinhibitory carotid-sinus reflex may be used as an aid in the diagnosis of coronary disease in persons of the coronary age who present suspicious complaints. As such, it is often of greater value than the electrocardiogram and will suggest the correctness of the diagnosis when the electrocardiogram may be entirely misleading.

The explanation for the frequency of the hyperactive reflex in coronary disease is at the present state of knowledge purely theoretical. It may be due to local ischemia in the heart, which lowers the resistance in the vagal ganglions and in the myoneural junctions, or which produces some chemical changes that sensitize the vagus nerves locally. AUTHORS.

**Langendorf, R., and Kovitz, B.: Acute Myocardial Infarction Without Deviation of the S-T Segment in the Electrocardiogram.** Am. J. M. Sc. **204**: 239, 1942.

A case is reported with recent myocardial infarction, proven at autopsy, in which elevation of the S-T segment was absent in the electrocardiogram taken during the acute stage. The absence of involvement of the subepicardial myocardium over the infarcted area is considered as the possible cause for the atypical record.

Cases of recent myocardial infarction with delayed electrocardiographic signs also may represent such cases of infarction of the subendocardial layers without involvement of the subepicardial layers of the myocardium.

Other causes for absence of this electrocardiographic sign must be excluded before this interpretation is entertained. AUTHOR.

**Robb, R. C., and Robb, J. S.: Experimental Bundle Branch Block After Ablation of One or Both Ventricles.** Am. J. M. Sc. **204**: 313, 1942.

In order to record a QRS-T complex, the presence of the "free" (i.e., nonseptal) walls of either (or both) right or left ventricles is unnecessary.

Not even the right side of the septum depends entirely for its excitation on conduction pathways which first reach the papillary muscles at the apices and then turn back. It contracts with a normal S-A rhythm when such pathways are interrupted by the total ablation of the "free" portions of both right and left ventricles, i.e., impulses are conducted from the main branches directly to the septum.

These experiments have not proven definitely whether the electrocardiograms recorded from the isolated septum are due to excitation of the septal muscle alone or whether action currents passing in the right and left branches (whose peripheral expansions were amputated) also produce some effect.

Not only does electrical activity of the free wall of each ventricle affect the electrocardiogram, but various portions of each wall have a characteristic effect.

These experiments do not support the theory that an electrocardiogram is summation of only one dextro- and one levocardiogram.

That the amplitude of deflections increases when the contact surface of the heart diminishes suggests that normally there is considerable neutralization of current.

So-called "axis deviation" appears when less rather than more of a given ventricle is present. Hence it appears to be due to loss of electrical components, with consequent change in the algebraic sum.

Laboratory animals, dogs, cats and rabbits, conform to the newer or American terminology for bundle branch block; i.e., when the right side of the heart is anatomically and functionally absent, there is a deep wide $S_1$ and a tall wide $QRS_3$. The reverse is true for anatomic and functional absence of the whole left ventricle.

AUTHORS.

**Sabathié, L. G., Gaspary, F., and Voogd, M.: Complete Auriculoventricular Block and Auscultable Auricular Flutter With Phonocardiographic Registration.** Rev. argent. de cardiol. **9**: 51, 1942.

A case of auscultable auricular flutter and auriculoventricular block with auricular flutter is presented in which the diagnosis was made clinically.

The frequency of this combination, its clinical diagnosis and the probable origin of the auricular sounds in flutter are discussed.

AUTHORS.

**Danelius, G.: Absence of the Hilar Shadow. A Diagnostic Sign in Rare Congenital Cardiac Malformations (Truncus Arteriosus Solitarius With Heterotopic Pulmonary Blood Supply).** Am. J. Roentgenol. **47**: 870, 1942.

A case of right-sided truncus aorticus solitarius with heterotopic pulmonary blood supply is analyzed anatomically and roentgenographically. The absence of the hilar shadow in the roentgenogram is explained through the absence or the marked underdevelopment of the right and left pulmonary artery. The pulmonary circulation in these cases is maintained through the patent distal part of Botallo's duct, through supernumerary bronchial arteries or through a branch of a subclavian artery. The roentgen diagnosis of this condition can be made when absence of the hilar shadows is associated with a deep depression at the site of the pulmonary conus.

WILLIAMS.

**Goldburgh, H. L., Baer, S., and Lieber, M. M.: Acute Bacterial Endocarditis of the Tricuspid Valve.** Am. J. M. Sc. 204: 319, 1942.

The relative incidence of acute bacterial endocarditis of the tricuspid valve was considered. In 26,007 necropsies, 646 cases of acute bacterial endocarditis occurred. The mitral valve alone was involved in 47.6 per cent cases, the aortic valve alone in 25.4 per cent, and the tricuspid alone in 3.1 per cent. Involvement of the right side of the heart whether alone or in combination with other valve lesions, was found in 8.2 per cent cases.

Twenty cases in which the endocarditis was restricted to the tricuspid valve were studied. Of these 20 cases, nine were due to the pneumococcus. The pneumococcus is more apt to produce right-sided acute bacterial endocarditis, for nine (14.5 per cent) of 62 cases of pneumococcic endocarditis were restricted to the tricuspid valve as contrasted to the 3 per cent of 646 cases mentioned above.

Emphasis is placed upon the lack of diagnostic auscultatory findings in acute tricuspid bacterial endocarditis. In but eight of the twenty cases was mention made of any murmur being heard, and in none of these was the murmur found over the tricuspid area.

AUTHORS.

**Galvin, L. F.: The Virginia Program for Children With Rheumatic Fever.** The Child 6: 164, 1942.

The author describes briefly the activities of the Children's Bureau through Federal aid for cardiac children as a part of the application of the Crippled Children's Act. The state program in Virginia is well organized and may serve as an example to other states.

MCCULLOCH.

**Rakov, H. L., and Taylor, J. S.: Acute Disseminated Lupus Erythematosus, Without Cutaneous Manifestations and With Heretofore Undescribed Pulmonary Lesions.** Arch. Int. Med. 70: 88, 1942.

A consideration of the complex clinical manifestations of lupus erythematosus disseminatus is combined with the report of a case in which the patient exhibited pronounced pulmonary signs and lesions but showed no cutaneous eruptions at any time.

AUTHORS.

**Schroeder, H. A.: Studies on "Essential" Hypertension. IV. Early Arterial Hypertension.** Am. J. M. Sc. 204: 62, 1942.

Fifty patients exhibiting slight elevation of the blood pressure were studied with a view to ascertaining the varieties of clinical disturbance. Thirty-seven were found to be suffering from various diseases of the kidneys, and 11 others from dysfunctions of the nervous system. In addition, every patient exhibited nervous tension of some degree. In a few cases the onset of hypertension was associated with a definite physical or psychologic disturbance. It is probable in the light of this experience that arterial hypertension is the result of a number of factors, differing in different individuals.

AUTHOR.

**Markham, J. D., and Bloom, N.: The Significance of Electrocardiographic Changes in Malignant Hypertension.** J. Lab. & Clin. Med. 27: 1156, 1942.

In evaluating the significance of the electrocardiographic changes in malignant hypertension, a tabulation was made of the age at which each patient died. The greatest mortality was in the group 35 to 39 years old. The majority of deaths

occurred after the third decade was reached, while none occurred over 50 years of age. This indicates that the electrocardiogram is a reliable guide in following the progress of malignant hypertension and has some prognostic value. Senile degenerative changes, which may modify its usefulness, have not appeared. It is evident that the characteristic changes observed in this series are due solely to the effect of malignant hypertension on the heart.

AUTHORS.

**Thomas, C. B.: Experimental Hypertension From Section of Moderator Nerves: Relationship to Presence of Kidney Tissue.** Proc. Soc. Exper. Biol. & Med. **48**: 24, 1941.

The author attempted to establish by means of acute experiments whether antiotonin plays a role in the hypertension resulting from moderator nerve section. The results indicate that removal of both kidneys does not prevent the immediate appearance of a pressor response to moderator nerve section. It would seem that circulating pressor substances arising from the kidney are not demonstrably important in the production of acute neurogenic hypertension.

KERSHBAUM.

**Megibow, R. S., Katz, L. N., and Rodbard, S.: The Mechanism of Arterial Hypertension in Experimental Hydronephrosis.** Am. J. M. Sc. **204**: 340, 1942.

Complete unilateral ureteral occlusion in uninephrectomized dogs and complete bilateral ureteral occlusion are followed by a rise in the systemic arterial blood pressure which persists until the animals die of uremia.

Partial bilateral and complete or partial unilateral ureteral occlusion are followed by a transient elevation of the arterial blood pressure.

The addition of unilateral hydronephrosis to contralateral renal ischemia intensifies any tendency to hypertension. This indicates that the hydronephrotic kidney is actively concerned in the genesis and maintenance of arterial hypertension.

Evidence is presented that this mechanism is twofold, in that ischemia and destruction of normal renal tissue probably proceed simultaneously in the same kidney, the initiating factor being a rise in ureteral and intratubular pressure.

An explanation is offered for the occasional occurrence of normotension and renal excretory insufficiency observed in hydronephrosis.

AUTHORS.

**Foà, P. P., Foà, N. L., and Peet, M. M.: Effect of Pregnancy on Experimental Renal Hypertension in Rats.** Am. J. M. Sc. **204**: 350, 1942.

The normal systolic blood pressure of the young adult albino rat was found to average 85 mm. Hg (60 to 130). It is slightly lower during the summer.

Ether anesthesia has no appreciable effect on the systolic blood pressure of normal rats.

Systolic blood pressure in rats does not change significantly during normal pregnancy.

Hypertension of several months' duration can be produced in rats by constricting one renal artery without damage to the general health of the animal.

The systolic blood pressure of rats with hypertension due to the constriction of one renal artery is sharply reduced during pregnancy from an average maximum of 174 to an average minimum of 103 mm. Hg.

After delivery the systolic blood pressure again rises to hypertensive levels, reaching an average of 180 mm. Hg.

Constriction of the renal artery of pregnant rats is followed by rapid decline and death. Hypertension may or may not occur.

The influence of pregnancy on experimental renal hypertension in rats is discussed. It is suggested that the drop in blood pressure might be due to an endocrine mechanism.

AUTHORS.

**Saxton, J. A., Jr.: Elastic Properties of the Rabbit Aorta in Relation to Age.** Arch. Path. 34: 262, 1942.

A study has been made of the elastic properties and morphologic character of the rabbit aorta at different ages (6 months to 5 years) and at three levels (upper, middle and lower regions of the descending thoracic portion). Segments (rings) of aorta, cut 5 mm. in length, from the three levels were subjected to increasing loads up to 180 Gm., and changes in their circumferences with and without loads were measured. From these measurements ratios of extension to original circumference, retraction to extended circumference and increase in circumference after unloading to original circumference were calculated. These ratios were compared graphically and as values of moduli at corresponding stresses in relation to age and to the level from which the segments were taken.

With advance in age the rabbit aorta becomes more extensible, shown by increasing values of the ratio of extension to original circumference and by decreasing values of Young's modulus at corresponding loads.

At the maximum load used the ratio of extension to original circumference was 124 per cent at 6 months and 152 per cent at 5 years.

No change in the capacity to retract after extension, expressed as the ratio of retraction to extended circumference, was observed in relation to age. At the maximum load used this ratio varied between 50 and 55 per cent.

With advance in age the rabbit aorta becomes less able to return to its original circumference after stretching, evidenced by increasing values of the ratio of increase in circumference after unloading the maximum load to original circumference (from 6 per cent at 6 months to 24 per cent at 5 years) and by decreasing values of the modulus for this relation at corresponding loads.

With advance in age the smooth muscle of the media is gradually replaced by collagenous tissue and there is an increase in fine elastic fibrils between the elastic membranes. The aortas of old rabbits, judged by measurements and by the waviness of the elastic membranes, appear slightly contracted in their post-mortem state as compared with aortas of young rabbits, and these differences may be associated with differences in the elastic properties.

The upper portions of the aorta were capable of more extension and retraction than the lower portions under comparable conditions.

The observed changes in elastic properties suggest that the rabbit aorta, in contrast to the human aorta, does not age so rapidly as compared with other organs and is still a relatively young structure at the end of the life span.

AUTHOR.

**Chapman, E. M., and Asmussen, E.: On the Occurrence of Dyspnea, Dizziness, and Precordial Distress Occasioned by the Pooling of Blood in Varicose Veins.** J. Clin. Investigation **21**: 393, 1942.

The authors believe that undue fatigue, shortness of breath, dizziness, fainting, and precordial distress may be occasioned by pooling of blood in varicose veins. These clinical investigations offer evidence that the circulatory efficiency is decreased by such extensive pooling and that removal of this peripheral blood reservoir restores the hemodynamics of the subjects toward normal and relieves their symptoms.

AUTHORS.

**Wolf-Heidegger, G.: Concerning the Finding of Valves in the Veins of the Small Intestine.** Cardiologia 5: 359, 1941.

Valves were able to be demonstrated in the veins of the small intestine of various small mammals (dog, cat, rabbit, rat, mouse).

Of the kinds of animal examined, the dog and the cat possess the most and largest vein valves. Age differences were not observed.

Vein valves are present in the first extraintestinal portion of the mesenteric veins in the immediate vicinity of the mesenteric border, in the large veins perforating the muscular layers and in the vein system of the lamina intermuscularis.

The importance of these valves is discussed.

AUTHOR.

**Hertzman, A. B., and Roth, L. W.: The Absence of Vasoconstrictor Reflexes in the Forehead Circulation. Effects of Cold.** Am. J. Physiol. 136: 692, 1942.

The absence of vasoconstrictor reflexes in the forehead is demonstrated by the following evidence:

The spontaneous rhythmic constrictions of vasomotor origin in the finger of the resting subject are absent from the forehead.

The vasoconstrictor reflexes elicited by startle, awakening, a deep breath, immersion of the hand in ice water or local cold to the forehead are wholly absent in the latter.

The vascular reactions of the forehead skin to local cold are like those of a sympathectomized digit. Constriction is gradual as the temperature of the skin falls and seems to be due to the direct effects of cold on the vessels.

The reactive dilatation to cold which occurs in the fingers, was not observed in the forehead skin.

Occasionally, there was indication of a vasodilator reflex in the forehead skin at the time of a powerful constriction in the finger.

AUTHORS.

**Gregg, D. E., Shipley, R. E., Eckstein, R. W., Rotta, A., and Wearn, J. T.: Measurement of Mean Blood Flow in Arteries and Veins by Means of the Rotameter.** Proc. Soc. Exper. Biol. & Med. 49: 267, 1942.

The rotameter has been adapted to the measurement of mean blood flows in arteries and veins and also in cardiac input. A description of the apparatus is given and the proper methods of its use, sources of error and procedures for calibration are discussed. Typical records are shown. Tests indicate that in routine use the instrument will measure blood flow with an error of less than 10 per cent. An advantage over other methods of measuring blood flow is that the experimenter can determine at a glance the moment to moment flow during the time that flow is actually being measured.

WILLIAMS.

**Davis, H. A., and Eaton, A. G.: Comparative Effects of Horse Serum, Horse Serum Albumin and Horse Serum Globulin in Experimental Shock.** Proc. Soc. Exper. Biol. & Med. 49: 359, 1942.

The experiments were conducted on dogs under light ether anesthesia. Shock was produced by graded hemorrhage from the carotid artery. The sera were administered by gravity, through a cannula inserted into the right femoral vein, in amounts equal to the quantity of blood removed. The administration of whole serum caused a rise in blood pressure which was maintained and the animals recovered. Mild dyspnea was observed for a short time following the injection. The administration of serum globulin caused marked dyspnea. The three dogs

which survived showed moderate rise in blood pressure following the injection but were sick and listless for several days. The fourth dog died twelve hours after the injection and autopsy revealed subcutaneous, subserosal, subpleural, subepicardial and subendocardial hemorrhages, a congested liver and a contracted spleen. The administration of serum albumin resulted in a rise of blood pressure to almost the initial level which was maintained, and all of the animals recovered without after-effects. Horse serum albumin and serum globulin affect dogs in a manner similar to bovine serum albumin and serum globulin, while horse serum is less toxic than bovine serum. It is suggested that some substance in whole horse serum, possibly serum albumin, tends to diminish the toxicity of the globulin.

WILLIAMS.

**De Gowin, E. L., Harris, J. E., and Bell, J.: Rates of Hemolysis in Human Blood Stored in Dextrose Solutions and in Other Mixtures.** Proc. Soc. Exper. Biol. & Med. **49**: 481, 1942.

Hemolysis during storage at 2° C. is markedly inhibited by the addition of dextrose to blood-citrate mixtures. Maximal inhibition of hemolysis is obtained with a final concentration of dextrose of approximately 3 per cent and this mixture permits the safe storage of blood for about thirty days. Sucrose is not so effective as dextrose, and NaCl and KCl increase the rate of hemolysis.

WILLIAMS.

**Leinoff, H. D.: Acute Coronary Thrombosis in Industry: I. Direct Nonpenetrating Injuries, With Report of Cases.** Arch. Int. Med. **70**: 33, 1942.

Direct nonpenetrating injury of the chest can produce nonfatal disabling heart damage.

The resulting disability is due to a combination of structural and functional changes.

The clinical picture is that of an acute pathologic condition of the heart and closely resembles that of coronary occlusion, from which it is differentiated by the history.

The history is the most important single factor in determining causal relation and the subsequent degree of disability.

The electrocardiographic studies are important and usually show changes associated with acute lesions.

This clinical syndrome should be considered in the presence of any injury of the chest.

AUTHOR.

**Scherf, D., and McGavack, T. H.: The Estrogen-Like Action of Desoxycorticosterone Acetate Upon the Altered Electrocardiogram Seen in Various Hypo-Ovarian States.** Am. J. M. Sc. **204**: 41, 1942.

Six women with clinical manifestations of hypo-ovarianism and electrocardiographic changes, typical of such a state, have been described.

The influence of desoxycorticosterone acetate and ovarian follicular hormone on the clinical and electrocardiographic disturbances present in each 4 of these has been recorded and evaluated. In 2 additional individuals, changes following the administration of desoxycorticosterone acetate have been noted.

In each of the 4 patients to whom administered, estrogens returned the previously altered electrocardiogram to normal. Total dosages necessary for this effect varied from 14,000 to 50,000 international units.

In all 6 patients, the previously altered electrocardiogram reverted to normal under the influence of desoxycorticosterone acetate in total doses of 30 mg. to 60 mg. The response was equivalent in kind and in degree to that observed following the ad-

ministration of ovarian follicular hormone, provided proper dosages were employed.

Possible explanations of this action of desoxycorticosterone acetate upon the heart are discussed. Among these must be included a direct action by way of blood vessels and blood and tissue electrolytes, and an indirect action by way of other endocrine glands, notably the pituitary and the gonads.

AUTHORS.

**Ziskin, T., and Dumas, A. G.: Observations on the Electrocardiogram in Epilepsy and Comparison With Electrocardiogram in Seizures Following Convulsant Drug Therapy.** J. Lab. & Clin. Med. 27: 1249, 1942.

The electrocardiographic findings which the authors observed during and after epileptic seizures tend to show that cardiovascular changes occur following epileptic seizures, and that these changes are part of circulatory changes throughout the body. As a result of this, and from the experimental and clinical observations of other workers, the supposition is made that the epileptic seizures are due to a cerebral anoxemia resulting from an ischemia of the brain following vasoconstriction. This is probably the result of an electrochemical change and adrenalin-like action on the cerebral vessels.

After comparing their findings with those of other workers who studied the electrocardiographic changes following seizures after convulsant drug therapy, they conclude that the physiologic changes during and after convulsive seizures from excitant drugs are the same as those due to epilepsy; also that the extrinsic factors, such as insulin shock and metrazol, probably produce a similar adrenalin-like reaction as the intrinsic factor which brings on the cerebral ischemia and anoxemia in epileptic seizures.

AUTHORS.

**Futcher, P. H., and Schroeder, H. A.: Studies on Congestive Heart Failure. II. Impaired Renal Excretion of Sodium Chloride.** Am. J. M. Sc. 204: 52, 1942.

In 4 patients convalescent from severe congestive heart failure there was found an impairment of the ability of the kidney to excrete sodium and chloride (as compared to 2 subjects without heart disease), when the concentration of these ions in the serum was experimentally elevated above normal.

Mercurial diuretics increased the excretion of sodium and chloride by these same subjects.

AUTHORS.

**Hartwell, A. S., Burrett, J. B., Graybiel, A., and White, P. D.: The Effect of Exercise and of Four Commonly Used Drugs on the Normal Human Electrocardiogram, With Particular Reference to T Wave Changes.** J. Clin. Investigation 21: 409, 1942.

Exercise lowers the T waves of the normal human electrocardiogram, with return toward normal in less than a minute. During recovery the amplitude of T may be greater than normal.

Adrenalin lowers the T waves. The effect lasts from fifteen to thirty minutes.

Ergotamine tartrate raises the T waves. This effect lasts as long as an hour.

Atropine lowers the T waves. The effect is maximal in one hour but may last ninety minutes.

Mecholyl lowers the T waves and causes tachycardia without preliminary bradycardia.

Right carotid sinus pressure causes an elevation of the T waves.

The importance of taking these changes into account when interpreting electrocardiograms is stressed.

AUTHORS.

**Decherd, G. M., Jr., and Hermann, G. R.: The Results of Treatment of Various Cardiac Mechanism Disturbances.** Texas State J. Med. **37**: 767, 1942.

In 116 cases of this series, atrial or auricular fibrillation was present, 73 times in patients with hypertensive heart disease, 20 times in rheumatics, 15 times in syphilitics, 5 times in thyrotoxics, 1 was due to over-digitalization, and 3 were of unknown etiology. Only two cases were refractory to digitalis, and one of these seemingly became responsive after calcium administration. Quinidine sulphate restored normal sinus mechanism in 12 out of the 16 cases in which it was used.

Atrial flutter was studied in 25 cases, most of which were of hypertensive and arteriosclerotic heart disease. Digitalis was administered to produce fibrillation in 17 cases, and in 9 of these subsequent cinchonization was necessary to restore the normal sinus rhythm. Quinidine alone was successful in 9 out of 12 cases.

Paroxysmal atrial tachycardia was recorded in 27 hospital cases, 14 of whom had died of heart disease at the time of the summarization. Carotid sinus stimulation was effective in stopping the attack in 5 out of 8 cases; quinidine in 5 out of 6 cases; intravenous digitalis in 3 out of 5 cases; prostigmin in 1 out of 3 cases; morphine in 2 out of 2 cases.

Paroxysmal ventricular tachycardia was most serious; 7 of 8 cases had died; 3 out of 5 cases responded to quinidine. Adams-Stokes seizures were temporarily controlled in some cases by barium chloride, ephedrine, adrenalin in oil, thyroid extract and paredrine hydrobromide. Carotid sinus attacks were prevented by the use of belladonna or atropine.

AUTHORS.

**Chen, K. K., Bliss, C. I., and Robbins, E. B.: The Digitalis-Like Principles of Calotropis Compared With Other Cardiac Substances.** J. Pharmacol. & Exper. Therap. **74**: 223, 1942.

Of the three digitalis-like principles of Calotropis, their potencies relative to each other and to ouabain were in the following order when tested in parallel:

| Drugs in Anhydrous Form | In Frogs | In Cats |
|---|---|---|
| Ouabain | 144 | 121 |
| Calotropin | 100 | 100 |
| Calotoxin | 76 | 92 |
| Uscharin | 42 | 69 |

All differences were significant except that between calotropin and calotoxin in cats.

By simultaneous comparison of the above 4 drugs with 8 other cardiac principles in etherized cats, their potencies in anhydrous form relative to ouabain were convallotoxin 112, ouabain 100, $\beta$-antiarin 90, $\alpha$-antiarin 87, cymarin 86, calotropin 83, coumingine HCl 78, calotoxin 76, emicymarin 63, bufotalin 61, uscharin 58, and periplocymarin 55. Differences between pairs in the above series that are less than 18 per cent of the smaller potency cannot be considered significant.

For 10 of the above drugs, the median lethal dose had also been determined individually over a period of several years and in four cases the new values differed significantly from the earlier determinations, demonstrating the importance of parallel tests with group standards in experiments on the toxicity of cardiac substances to cats.

The lethal dose in cats showed a closer relation to the size of the heart, in terms of the two-thirds power of its fresh weight, than to the weight of the body, so that comparisons of drugs corrected for size of heart were the more precise and have been quoted in the summary. Due to the high correlation between heart weight and body weight, relative potencies determined by both procedures agreed within a small percentage.

AUTHORS.

**Chen, K. K., Steldt, F. A., Fried, J., and Elderfield, R. C.: The Action of Simple Lactones Related to Cardiac Aglycones.** J. Pharmacol. & Exper. Therap. 74: 381, 1942.

Twenty-seven unsaturated lactones related to cardiac aglycones have been studied pharmacologically.

$\beta$, $\gamma$-Angelica lactone, the lactone of 21-hydroxy-$\Delta^{20,22}$-norcholenic acid, methyl coumalate, and ethyl coumalate, cause systolic standstill of frogs' ventricles when adequate doses are injected into the ventral lymph sac. $\beta$-($\beta$-Naphthyl)-$\Delta\alpha,\beta$-butenolide has a suggestive action.

In cats, $\beta$, $\gamma$-angelica lactone and methyl and ethyl coumalates all produce a fall of blood pressure and fail to induce emesis. Electrocardiographically, no ectopic rhythm, multiple foci of impulse formation, various forms of aberrant QRS complexes, and terminal ventricular fibrillation occur as the lethal dose is slowly approached. The evidence in cats is therefore not indicative of any digitalis-like action of the three substances.

AUTHORS.

**Obreshkove, V.: Cardiac Inhibition of a Cladoceran and the Action of Acetylcholine and Physostigmine.** Proc. Soc. Exper. Biol. & Med. 49: 427, 1942.

The heart of *Daphnia magna* can be arrested by applying a mechanical stimulus to a region in the digestive tube where the stomach enters the intestine. The period of heart arrest varied from about 2.5 to 21 minutes. For several minutes after escape from inhibition the heart showed grouped beats which were feeble in character, irregular in amplitude and much slower than normal. Within less than 20 seconds after the addition of acetylcholine there was observed a sudden increase in the frequency of the heart beat, in some instances it was equal to or greater than the normal rate, and the cardiac activity became immediately more powerful and regularly rhythmic in character. If the animals were treated with physostigmine for a period of from 5 to 15 minutes before the cardiac inhibition was produced, the cardiac rhythm became regular and there was re-establishment of the normal rate of heart beat almost immediately after escape from inhibition.

WILLIAMS.

**Martin, G. J., and Hueper, W. C.: Biochemical Studies of Atheromatous Animals.** Proc. Soc. Exper. Biol. & Med. 49: 452, 1942.

Following the oral administration of cholesterol to rabbits or the parenteral administration of polyvinyl alcohol to dogs it was found that there was a decrease in the speed of oxygenation of the red cells. It is suggested that this effect is due to a coating action of the macromolecular compounds used. Plasma volumes increased approximately 100 per cent during the first twenty-four hours following injection of 50 c.c. of 5 per cent solution of polyvinyl alcohol. This osmotic activity is probably due to the slowness with which the colloid is removed from the blood and to its coating the intima with a film which may interfere with the escape of water from the liquid component of the blood.

WILLIAMS.

**Jacobson, S. D., and Smyth, C. J.: Plasma Volume Changes Following the Intravenous Injection of Pectin and Physiologic Saline in Man.** Proc. Soc. Exper. Biol. & Med. 50: 218, 1942.

The subjects for the experiments were 9 male patients who were normal with respect to the cardiovascular system. An average of 690 c.c. of 0.75 per cent pectin solution were injected intravenously in each of 5 patients at the rate of

10 c.c. per minute. 1000 c.c. of saline were injected intravenously in each of 4 patients. Plasma volume determinations were made before injection, at the end of infusion on 2 patients receiving each solution, 4 hours after the end of infusion on the other 5 patients, and 24 hours after the end of infusion on all patients. Immediately following the injection of pectin the plasma volume was increased by an amount equal to the volume of solution injected, 4 hours later the increase in volume was greater than that of the injected solution, and at the end of 24 hours there was an increased plasma volume in 3 patients. Immediately following the injection of saline solution the increase in plasma volume was considerably less than the volume of injected solution and was still less at the end of 4 hours, and the plasma volume had returned nearly to normal at the end of 24 hours.

WILLIAMS.

**Rath, M., and Krantz, J. C., Jr.: Nitrites. X. Effect of Sodium Nitrite Upon the Blood Pressure of Unanesthetized Hypertensive Rats.** Proc. Soc. Exper. Biol. & Med. 50: 248, 1942.

Systolic blood pressures in the tails of rats were determined by a plethysmographic method. Rats were rendered hypertensive by (a) subtotal nephrectomy or (b) bilateral wrapping of cellophane on the kidneys or (c) unilateral nephrectomy combined with unilateral cellophane wrapping. An oral dose of 4 mg. of sodium nitrite per 100 Gm. of body weight caused the blood pressure to drop from an average of 140 mm. to an average of 118 mm. in thirty minutes. Intraperitoneal injection of 2.5 mg. of sodium nitrite per 100 Gm. of body weight caused the blood pressure to drop from an average of 140 mm. to an average of 116 mm. in twenty minutes.

WILLIAMS.

**Hirschfelder, A. D., and Tamoales, G.: Inhibition of Experimental Auricular Fibrillation by Procaine and Other Substances.** Proc. Soc. Exper. Biol. & Med. 50: 272, 1942.

Auricular fibrillation in anesthetized dogs was produced either by faradic stimulation of the right auricle or by dropping acetyl beta methyl choline chloride solution onto the wall of the atrium. Ten to 20 mg. per kilo of procaine intravenously stopped fibrillation, produced by minimal effective faradic stimulation, for about five minutes. Forty to 80 mg. per kilo prevented fibrillation from maximal faradic stimulation. One to 6 mg. per kilo of procaine stopped fibrillation from being induced by acetyl beta methyl choline chloride solution within thirty-five seconds, the smaller doses of procaine being effective only for about five minutes. Similar effects in inhibiting auricular fibrillation were obtained with p-butyl amino-benzoyl-dimethyl amino-ethanol hydrochloride and with 2-butyloxyquinoline carboxylic acid-4-diethylethylene diamide hydrochloride.

WILLIAMS.

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**Corrigendum**

The abstract, "Idioventricular Rhythms and Fibrillation Induced at the Anode or the Cathode by Direct Currents of Long Duration," by Harris and Moe, page 271 of this number is a correction of an abstract of the same title appearing in the October number of this Journal, page 577.

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